

Obeticholic Acid (OCA)

Gastrointestinal Drugs
Advisory Committee Meeting

April 7, 2016

PBC: Diagnosis, Natural History and Role of Current Therapy

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Outline

- **Epidemiology**
- **Diagnosis**
- **Associated conditions**
- **Natural history**
- **UDCA Treatment**

PBC Newly Named

- **Primary Biliary Cirrhosis renamed to Primary Biliary Cholangitis**
- **Reflects earlier diagnosis: majority of patients without cirrhosis**
- **Name change endorsed by patient groups, physicians and societies (AASLD, EASL)**

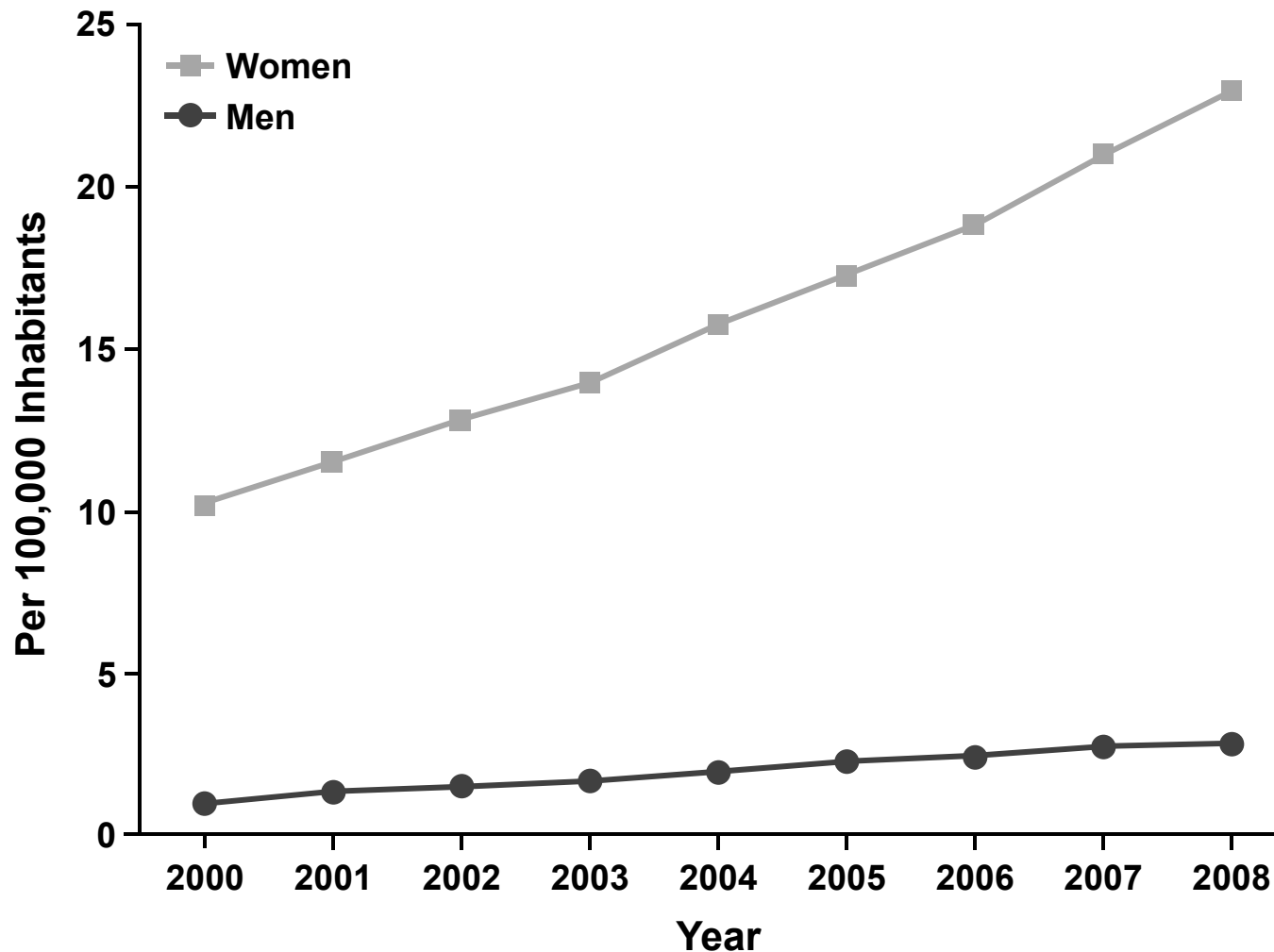
Causes and Markers of PBC

- **Autoimmune disease thought to be due to a combination of genetic predisposition and environmental triggers**
- **Lymphocytic inflammation targeting intrahepatic bile ducts**
- **Serologic hallmark of PBC is the AMA, a highly disease-specific autoantibody found in 90-95% of patients and less than 1% of healthy blood donors**
- **Serum biochemical tests show a cholestatic pattern**
 - ▶ Alkaline Phosphatase >> ALT/AST
 - ▶ Elevated serum bilirubin in late stage

Features of PBC

- **Chronic cholestatic disease with a progressive course which may extend over many decades**
- **Rate of progression varies greatly**
- **Asymptomatic in early disease**
- **Often leads to fatigue, pruritus**
- **Concomitant autoimmune diseases**
- **Affects about 1/1000 women age >40 years**
- **Is an important indication for liver transplantation in this population**

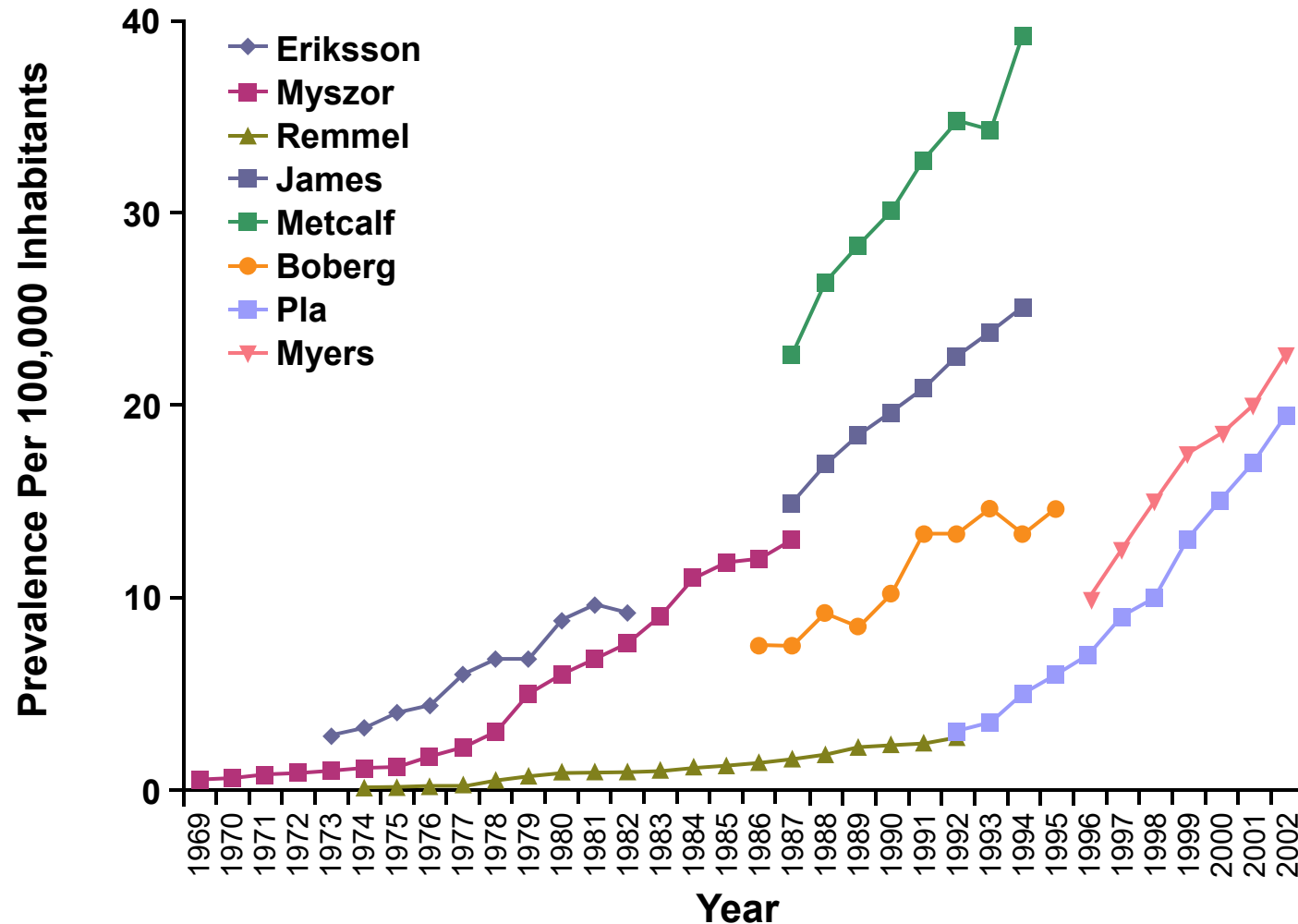
PBC Prevalence



Prevalence rates for the Netherlands

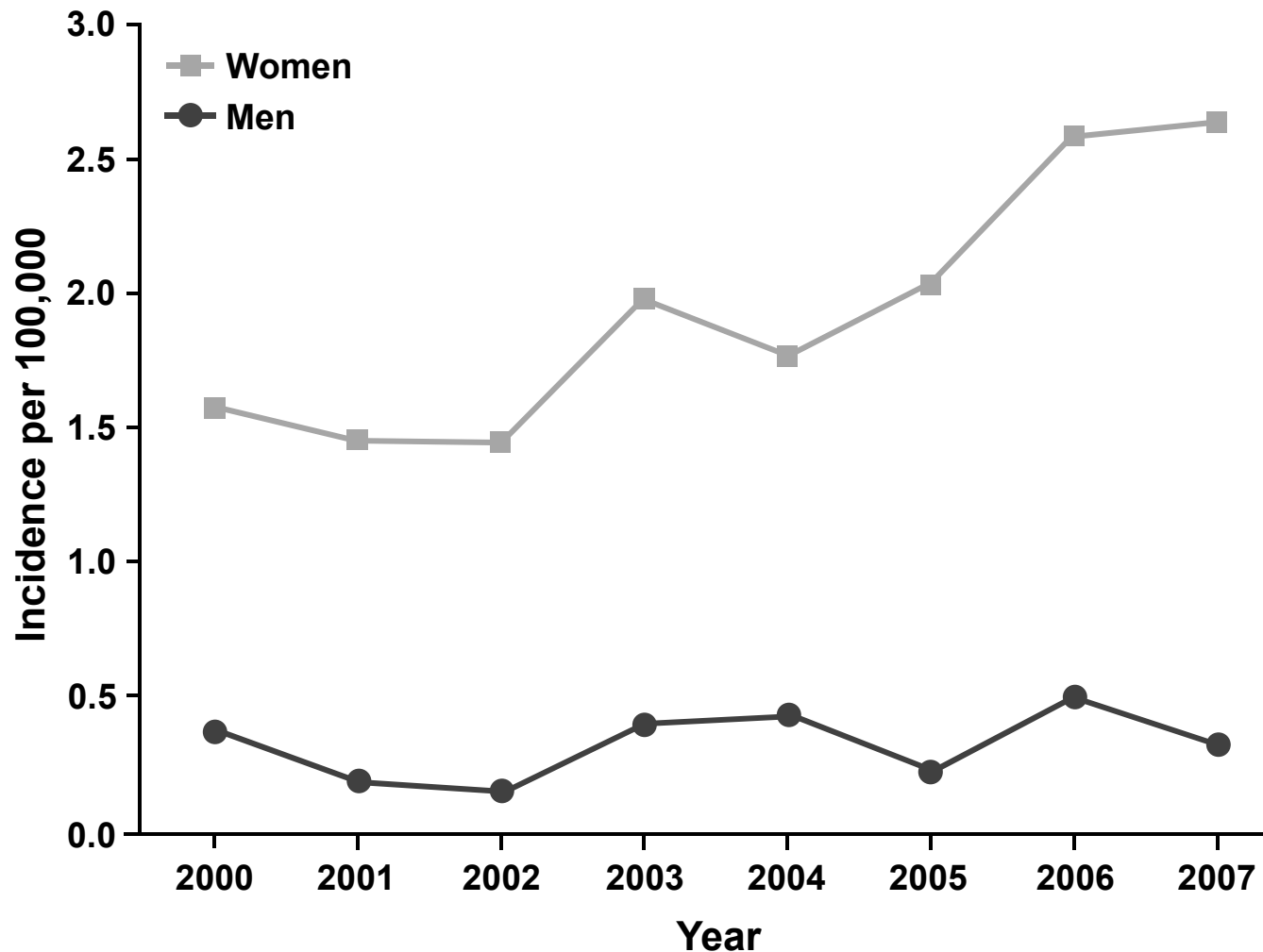
Boonstra K, Kunst A, Stadhouders P, et al. Rising Incidence and Prevalence of Primary Biliary Cirrhosis: A Large Population-base Study. *Liver International*. 2014;34:e35.

Global Temporal Trends in PBC Prevalence



Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: A systematic review. *Journal of Hepatology*. 2012; 56(5): 1181-1188.

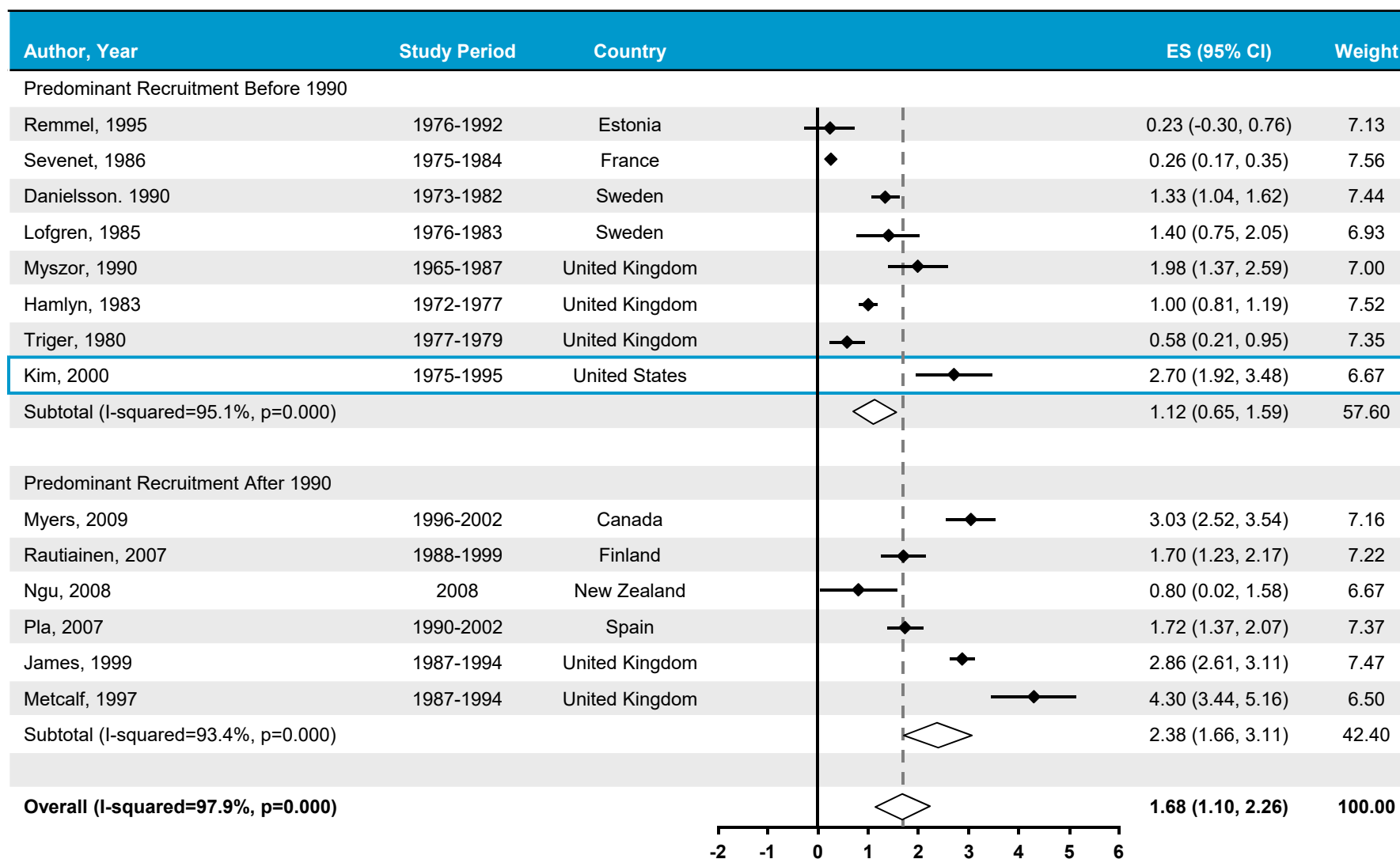
PBC Incidence



Prevalence rates for the Netherlands

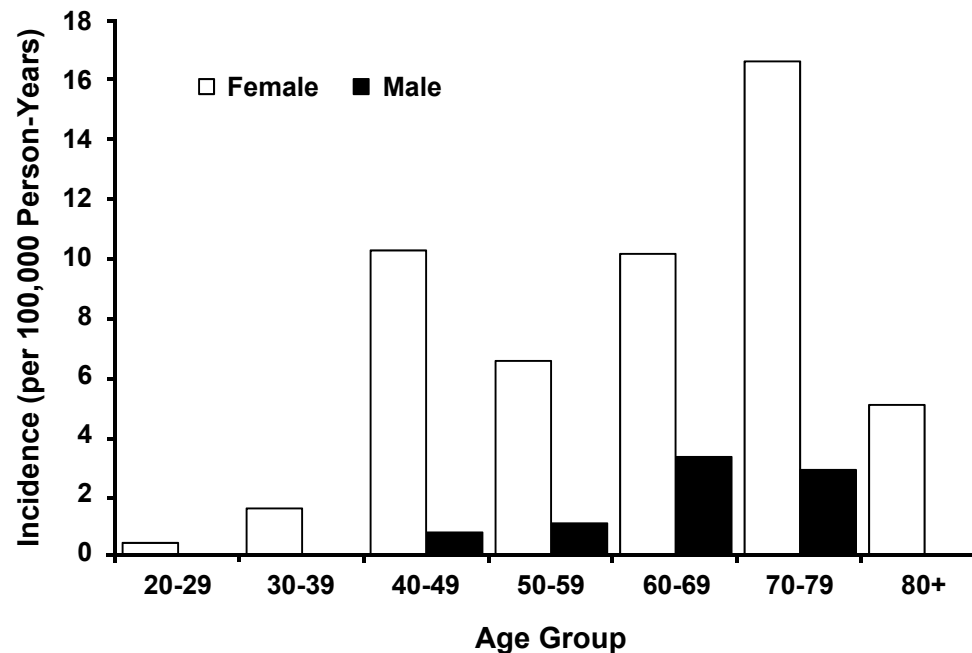
Boonstra K, Kunst A, Stadhouders P, et al. Rising Incidence and Prevalence of Primary Biliary Cirrhosis: A Large Population-base Study. *Liver International*. 2014;34:e35.

Incidence of Primary Biliary Cirrhosis: Systematic Review and Meta-analysis



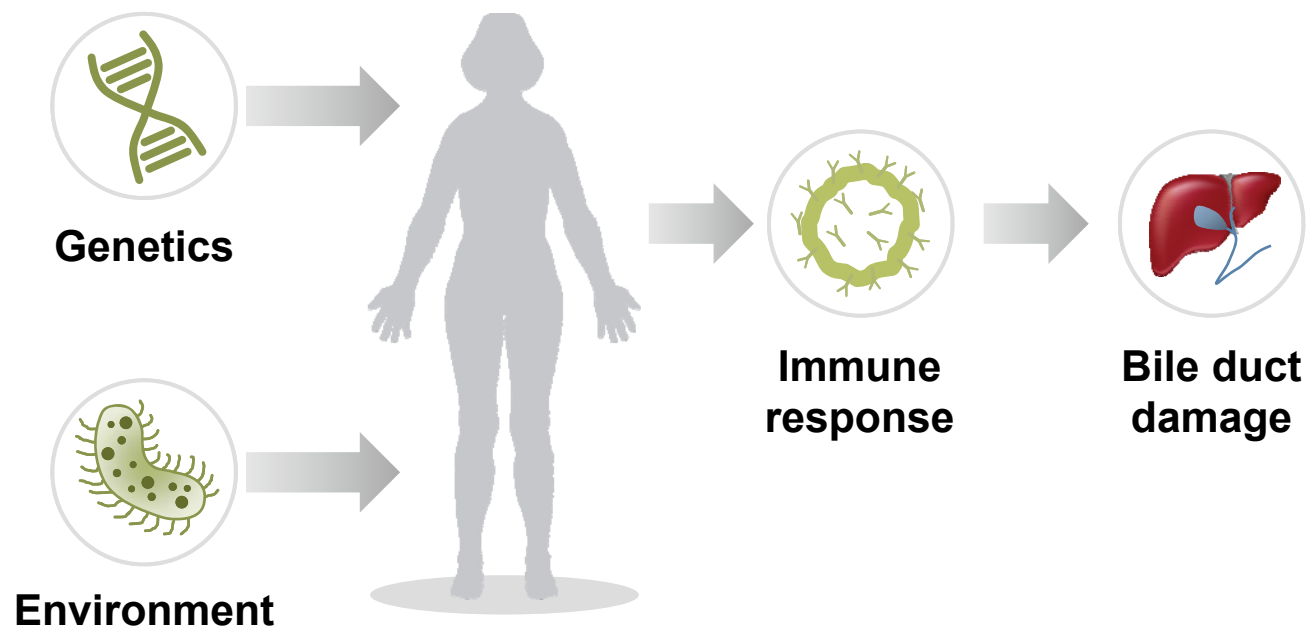
Incidence and Prevalence of PBC: Olmstead County, MN

- **Age-adjusted (1990 US whites) incidence/100,00: 2.7**
 - ▶ 1975-1995: women: 4.5 (3.1-5.9), men 0.7 (0.1-1.3)
- **Age and sex-adjusted prevalence (as of 1995): 40.2**
 - ▶ 65.4 (43-87.9) women, 12.1 (1.1-23.1) men



PBC is a Chronic, Progressive Autoimmune Disease

- Factors possibly associated with onset and perpetuation of bile-duct injury in PBC



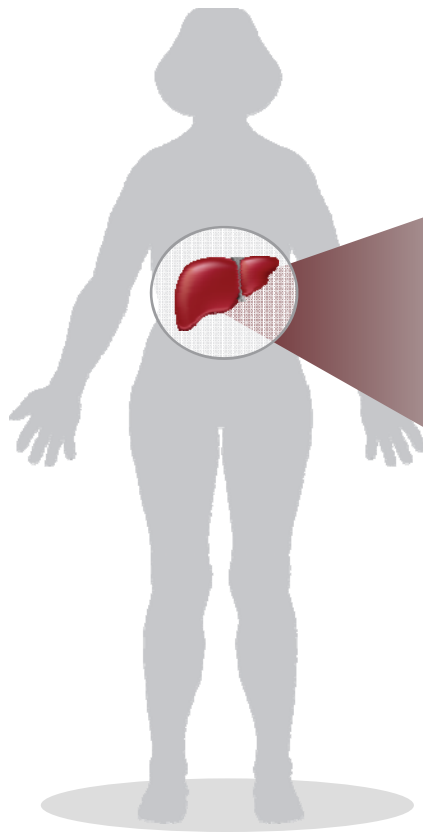
PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis

Concomitant Autoimmune Disease in Women with PBC

	Frequency (%)
Sjögren's syndrome	7-34
Raynaud's syndrome	9-13
Hashimoto's thyroiditis	11-13
Rheumatoid arthritis	3-8
Psoriasis	6
Scleroderma or CREST	1-2
Inflammatory bowel disease	1
Any autoimmune disease	33-55

CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome) is a limited type of scleroderma.

Clinical Features Vary Greatly Between Patients



Fatigue^{1,2}

Pruritus^{1,2}

Concurrent autoimmune diseases^{1,2}

Reduced bone density^{1,2}

Hypercholesterolemia^{1,2}

PBC can range from asymptomatic and slowly progressive to symptomatic and rapidly evolving.¹

¹Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609.

²Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575.

Pruritus Is Common Among PBC Patients

- **Prevalence reported as high as 69%¹**
- **Unknown etiology^{1,2}**
 - ▶ Bile salts, endogenous opioids, histamine, serotonin, progesterone/estrogen, and autotaxin/lysophosphatidic acid are suspected pruritogens²
- **Diurnal variation – most intense itch in the late evening²**
- **Localization reported at limbs – soles of feet, palms of hands²**
- **Exacerbated by pregnancy or contact with wool/heat³**

1. Imam MH, et al. *J Gastroenterol Hepatol*. 2012;27(7):1150-1158.

2. Beuers U, et al. *Hepatology*. 2014;60(1):399-407.

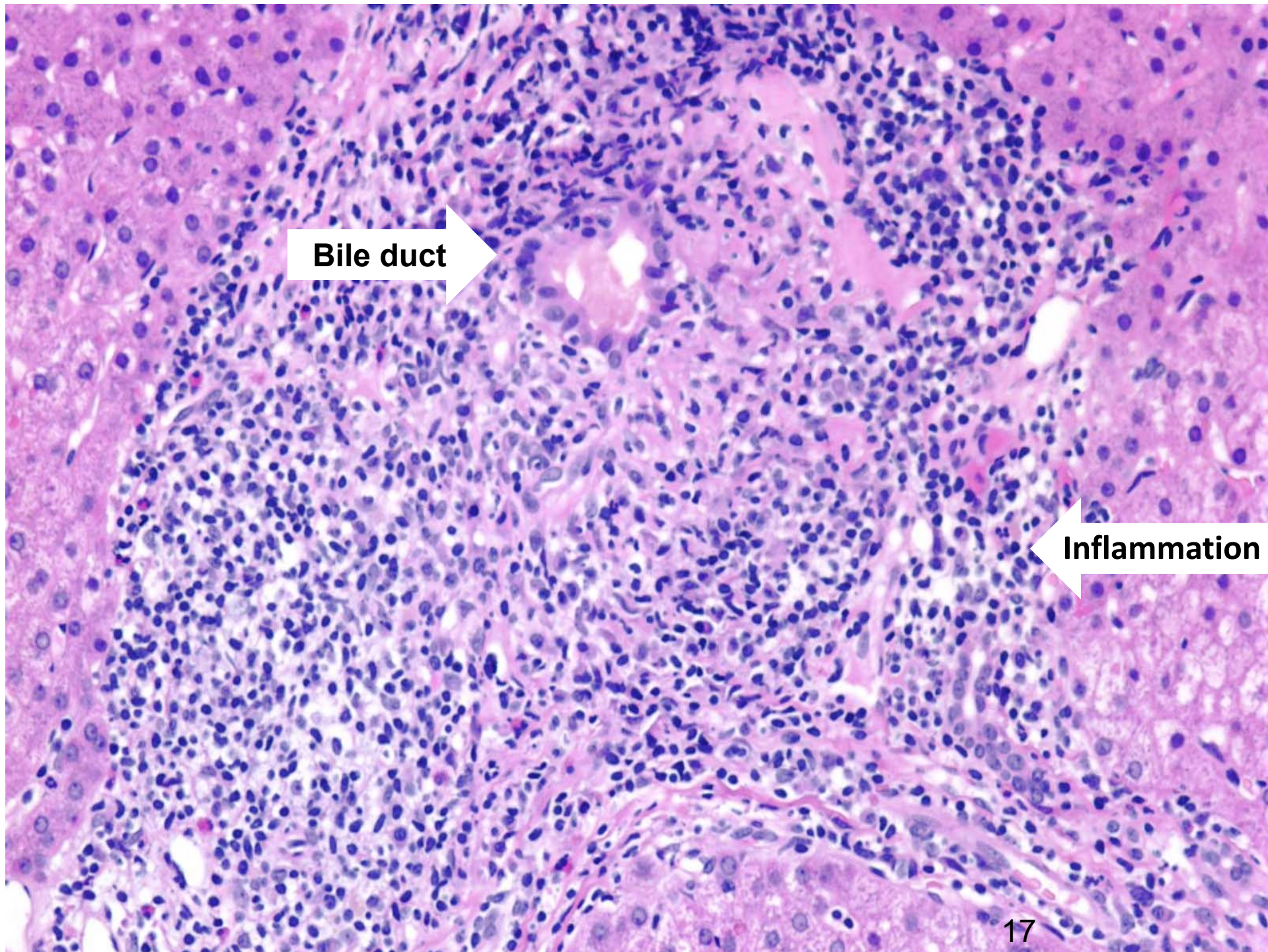
3. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

Numerous Treatment Options Exist to Help Patients Manage Their Pruritus

General Recommendations¹	<p>Skin moisturizer</p> <p>Wet, cooling, or moist wraps</p> <p>Topical agents with symptomatic relief (eg, camphor, menthol)</p> <p>Relaxation techniques</p> <p>Training to stop the cycle of itch, scratch, itch</p>
First-line²⁻⁴	<p>Bile acid sequestrants</p> <ul style="list-style-type: none"> • Cholestyramine • Colestipol, colesevelam
<i>The following agents may be used for pruritus that is refractory to bile acid sequestrants</i>	
Second-line²⁻⁴	<p>Rifampicin</p>
Third-line²⁻⁴	<p>Oral opioid antagonists</p> <ul style="list-style-type: none"> • Naltrexone • Nalmefene
Fourth-line²⁻⁴	<p>Selective serotonin reuptake inhibitors:</p> <ul style="list-style-type: none"> • Sertraline

1. Weisshaar E, et al. *Acta Derm Venereol.* 2012;92(5):563-581. European Association for the Study of the Liver. *J Hepatol.* 2009;51(2):237-267.

2. Lindor KD, et al. *Hepatology.* 2009;50(1):291-308. 4. Hohenester S, et al. *Semin Immunopathol.* 2009;31(3):283-3



Bile duct

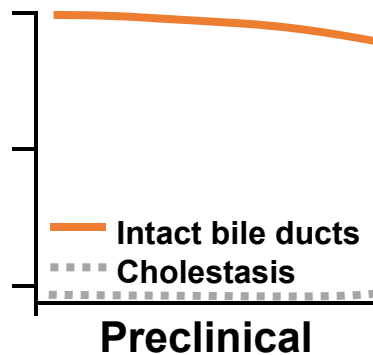
Inflammation

Diagnosis of PBC: Is Biopsy Needed?

- **If:**
 - ▶ \oplus AMA
 - ▶ ALP >1.5x ULN
 - ▶ AST <5x ULN
- **Then:**
 - ▶ Positive predictive value for PBC >98%
 - Sensitivity 80%, specificity 92%

PBC Disease Progression: Preclinical Stage

Disease Progression by Stage^{1,2}



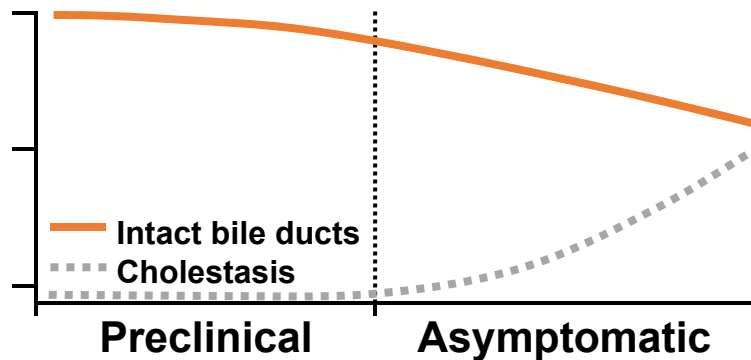
Graphic adapted from Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609.

1. Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609.

2. Silveira MG, et al. *Hepatology*. 2010;52(1):349-359.

PBC Disease Progression: Asymptomatic Stage

Disease Progression by Stage^{1,2}



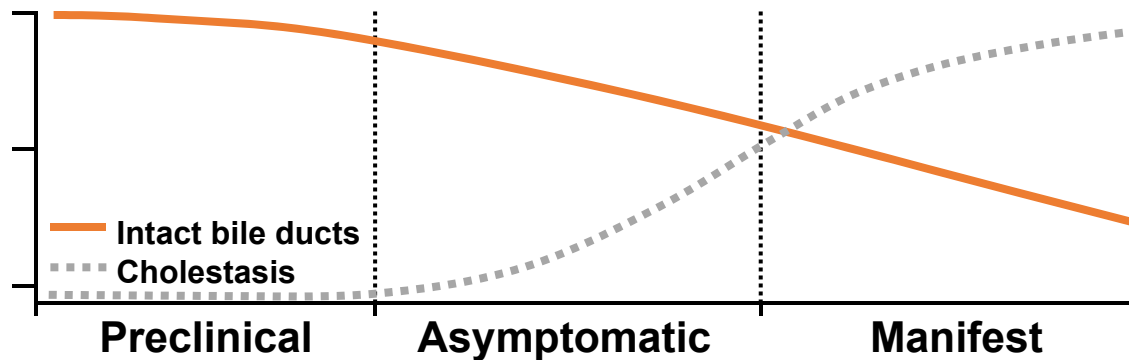
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1. Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609.

2. Silveira MG, et al. *Hepatology*. 2010;52(1):349-359.

PBC Disease Progression: Manifest Stage

Disease Progression by Stage^{1,2}



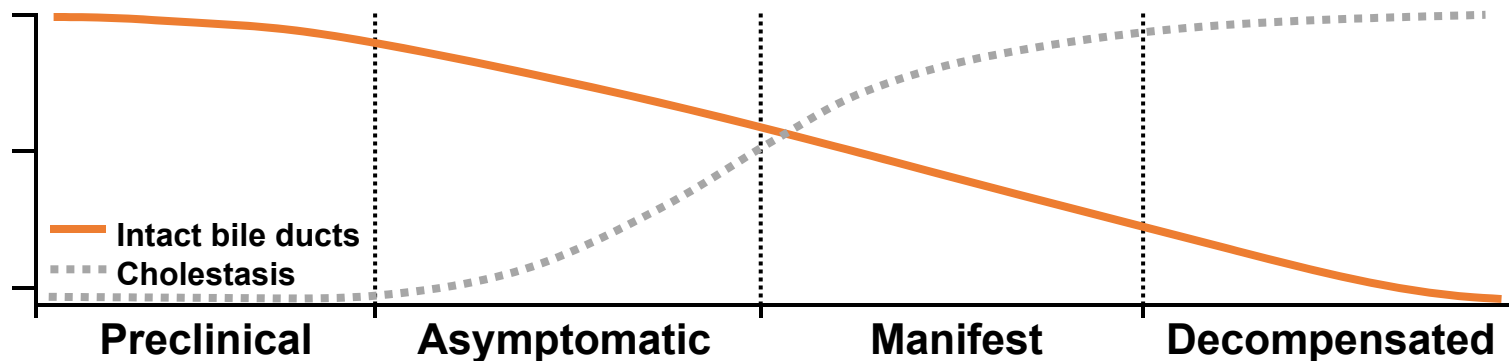
Graphic adapted from Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609.

1. Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609.

2. Silveira MG, et al. *Hepatology*. 2010;52(1):349-359.

PBC Disease Progression: Decompensated Stage

Disease Progression by Stage^{1,2}



Without intervention

- A substantial number of patients progress to liver failure, transplant, or death within 10 years²

Graphic adapted from Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609.

1. Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609.

2. Silveira MG, et al. *Hepatology*. 2010;52(1):349-359.

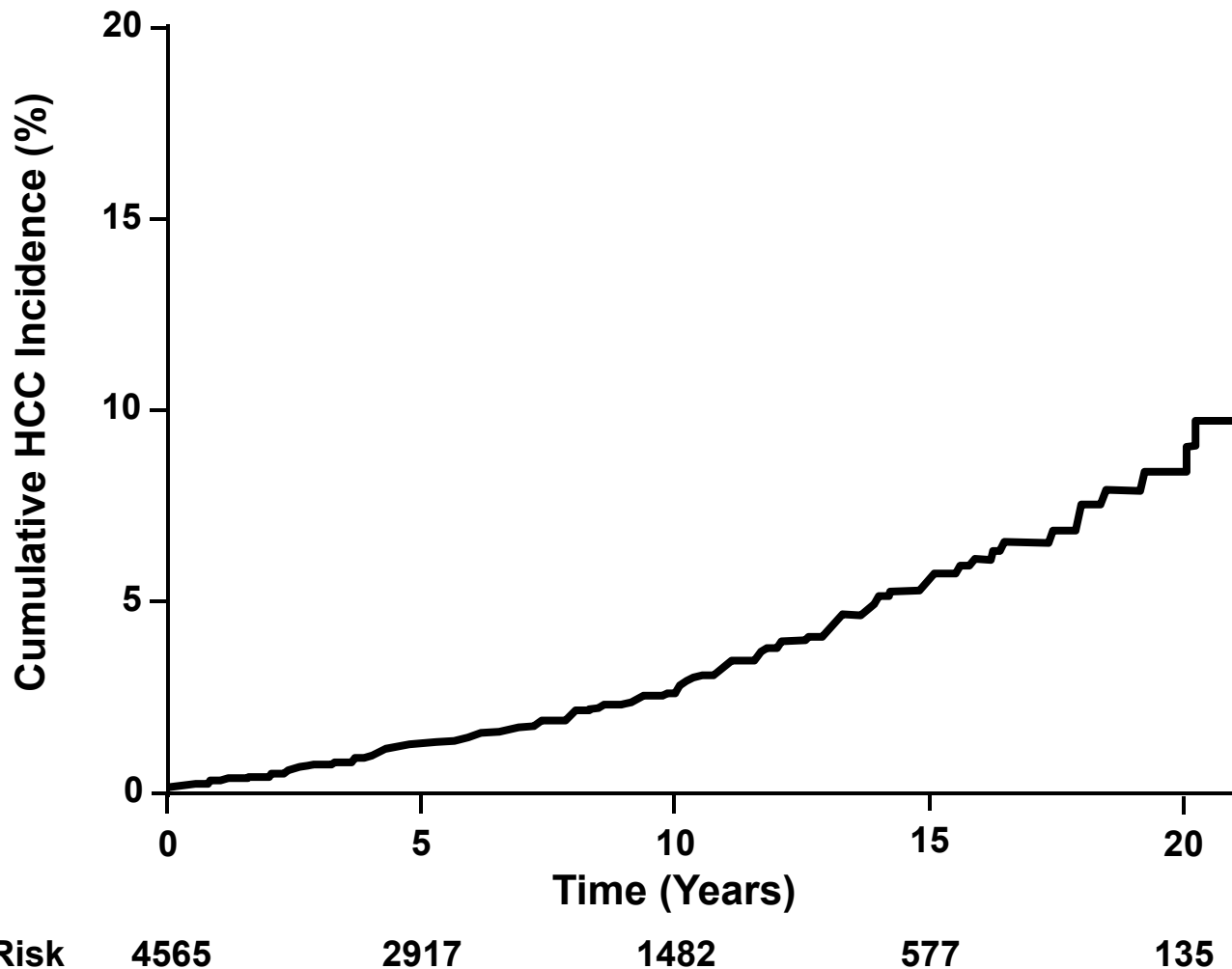
Many Patients With PBC Also Suffer from Cholestasis- and/or Cirrhosis-Associated Complications

% of Patients Affected	
Complications of chronic cholestasis¹	
Osteoporosis	20%-44%
Hyperlipidemia	75%-95%
Vitamin deficiency	8%-33%
Complications related to cirrhosis	
Varices associated with portal hypertension	6%
	(with early-stage disease) ¹
	~31%
	(with late-stage disease) ²
Hepatocellular carcinoma	1%-6% of patients per year ¹

¹Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575.

²Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

Hepatocellular Carcinoma in PBC: Global PBC Study Group



Time (0) is time of diagnosis or initiation of UDCA

Trivedi P, Lammers W, van Buuren, et al. *Stratification of hepatocellular carcinoma risk in primary biliary cirrhosis: a multicentre international study.* Gut. 2015; 0:1-9

Long-term Monitoring of Patients with PBC (AASLD Guidelines)

- Liver tests every 3-6 months
- Thyroid status (TSH) annually
- Bone mineral densitometry every 2-4 years
- Vitamins A, D, K annually if bilirubin >2.0
- Upper endoscopy every 1-3 years if cirrhotic or Mayo risk score >4.1
- Ultrasound ± AFP every 6 months in patients with known or suspected cirrhosis

Ursodeoxycholic Acid (UDCA)

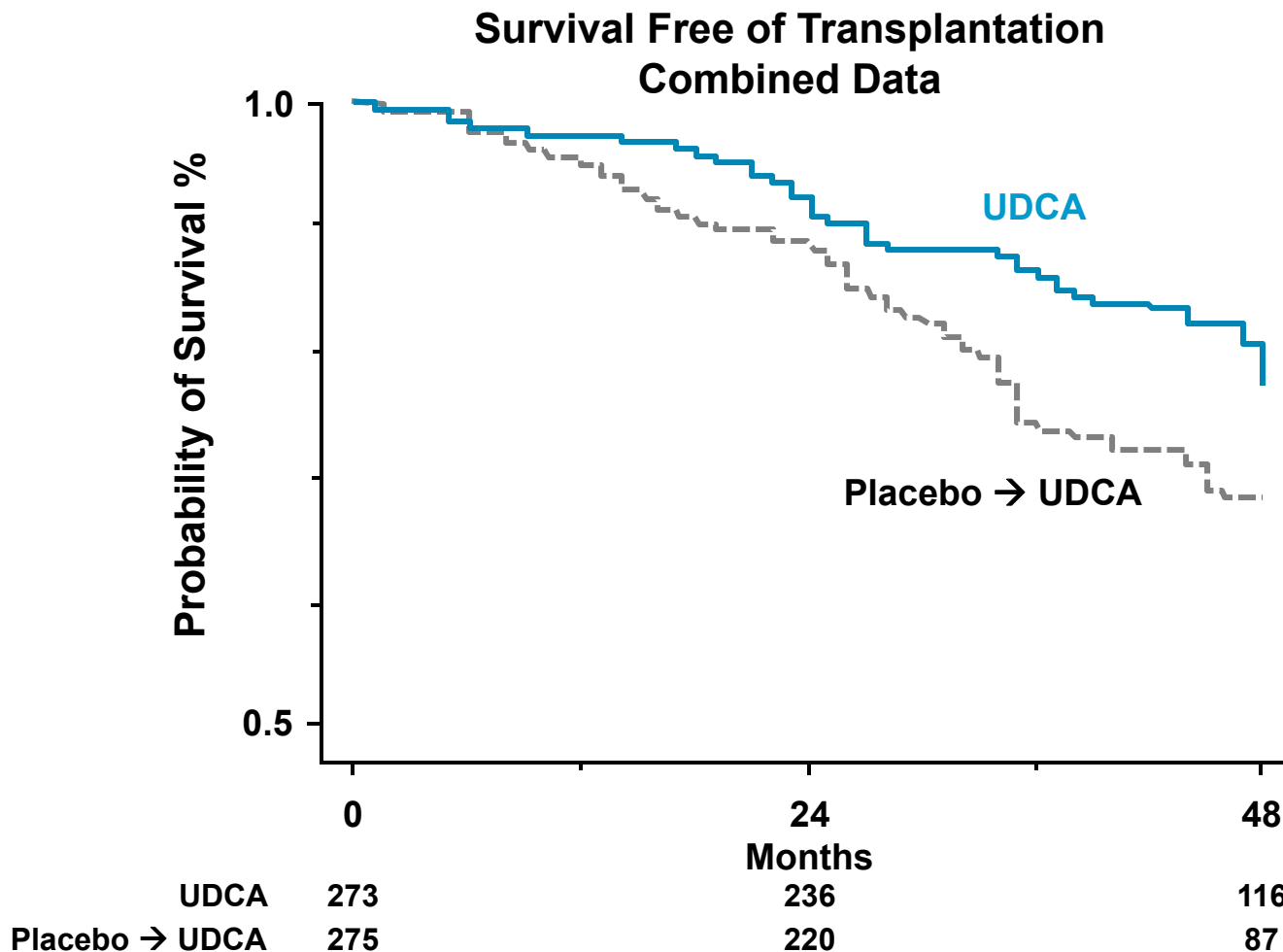
- **Approved in 1997**
- **Orally administered hydrophilic bile acid**
- **Preferred dose of 13-15 mg/kg/day**
- **Is the only currently FDA approved therapy for PBC**
- **Improvement in liver biochemistry (ALP) seen within a few weeks**
- **90% of the improvement usually occurs within 6-9 months**
- **However, up to 40% of PBC patients treated with UDCA have a suboptimal response**

Lindor KD, et al. *Hepatology*. 2009;50(1):291-308

Czul F, Levy C. *Clin Liver Dis* 2016;(1):113-30

Lammers WJ, et al. *Gastroenterology*. 2014 Dec;147(6):1338-1349

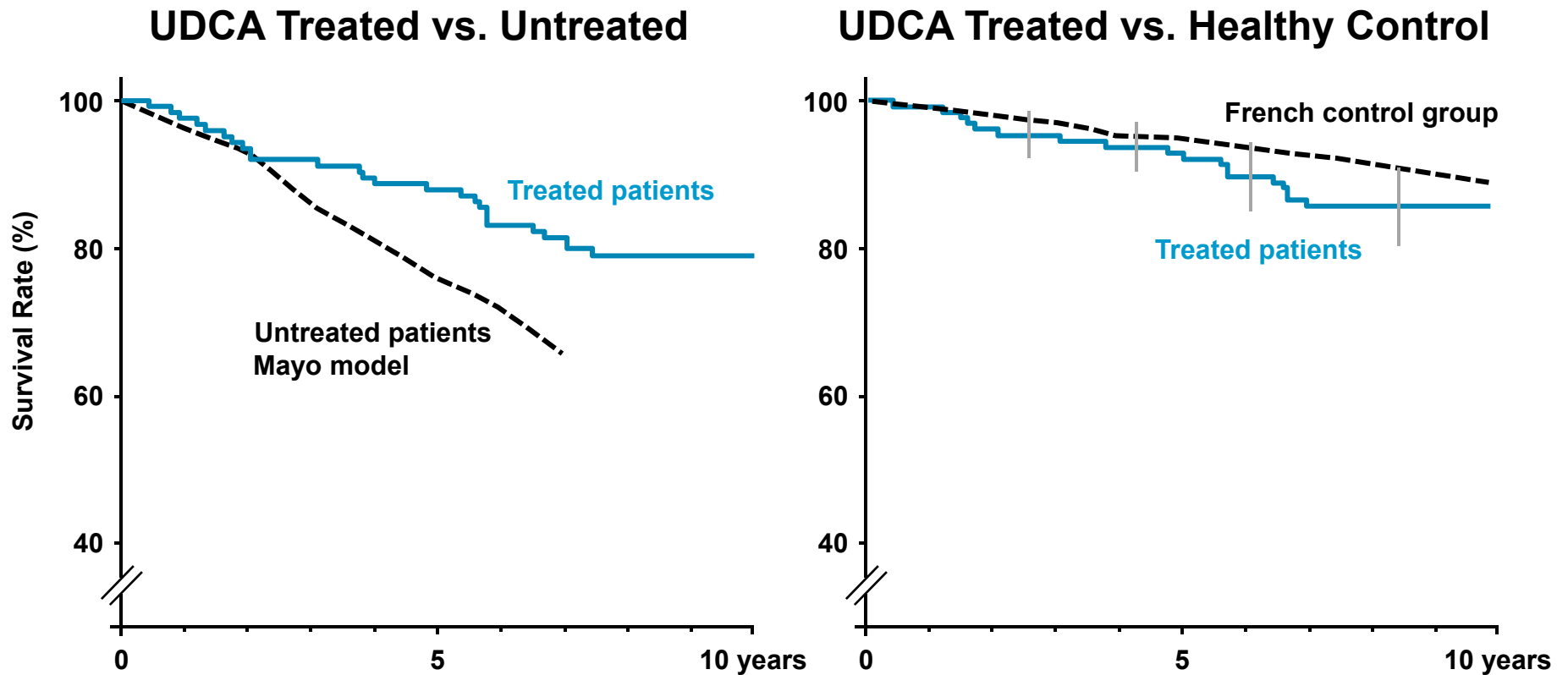
Medical Approaches to PBC: UDCA



* For the “Placebo → UDCA” group, patients randomized to placebo in 2 of the 3 pooled studies were treated with placebo for 2 years and then given the option to receive UDCA for an additional 2 years.

Poupon RE, Lindor KD, Cauch-Dudek K, et al. Combined Analysis of Randomized Controlled Trials of Ursodeoxycholic Acid in Primary Biliary Cirrhosis. *Gastroenterology*. 1997; 113:884-890

Survival in PBC: UDCA



Poupon RE, Bonnard AM, Chretien Y, et al. Ten-year survival in ursodeoxycholic acid-treated patients with primary biliary cirrhosis. The UDCA-PBC Study Group. Hepatology 1999; 29(6):1668-1671

Current (2009) Treatment Guidelines Vary

AASLD Guidelines (2009)¹

- **No specific definition or guidance of treatment success**
- “About 20% of patients will have normalization of liver biochemistries after 2 years and a further 15% or 35% of the total will have normalization by 5 years. The effect of treatment can be based on response of serum alkaline phosphatase activity or Mayo risk score, which is dependent on age, albumin, bilirubin, prothrombin time, and presence or absence of fluid retention”

EASL Guidelines (2009)²

“Recommendations”:

- Favorable long-term effects of UDCA are observed in patients with early disease and in those with good biochemical response (II-2/B1), which should be assessed after one year. **A good biochemical response after one year of UDCA treatment is currently defined by a serum bilirubin ≤ 1 mg/dL (17 μ mol/L), alkaline phosphatase ≤ 3 x ULN and AST ≤ 2 x ULN (“Paris criteria”) or by a decrease of 40% or normalization of serum alkaline phosphatase (“Barcelona criteria”) (II-2/B1)**

AASLD = American Association for the Study of Liver Diseases; AP = Alkaline phosphatase; EASL = European Association for the Study of the Liver.

1. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

2. European Association for the Study of the Liver. *J Hepatol*. 2009;51(2):237-267.

Response Criteria Models

ALP with or without bilirubin

**Barcelona¹
(2006)**

**Toronto⁴
(2010)**

**Early
Biochemical
Response⁶
(2013)**

**Paris-I²
(2008)**

**Paris-II⁵
(2011)**

Albumin and bilirubin

**Rotterdam³
(2009)**

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1. Parés A, et al. *Gastroenterology*. 2006;130:715-720. 2. Corpechot C, et al. *Hepatology*. 2008;48:871-877. 3. Kuiper EM, et al. *Gastroenterology*. 2009;136:1281-1287. 4. Kumagi T, et al. *Am J Gastroenterol*. 2010;105:2186-2194. 5. Corpechot C. *J Hepatol*. 2011;55:1361-1367. 6. Zhang LN, et al. *Hepatology*. 2013;58:264-272.

Current Response Criteria Models

Biochemical + APRI¹ (2014)

Biochemical response (Barcelona, Paris-I/II, or Toronto) and APRI ≤ 0.54 after 1 year UDCA

UK-PBC Risk Score² (2015)

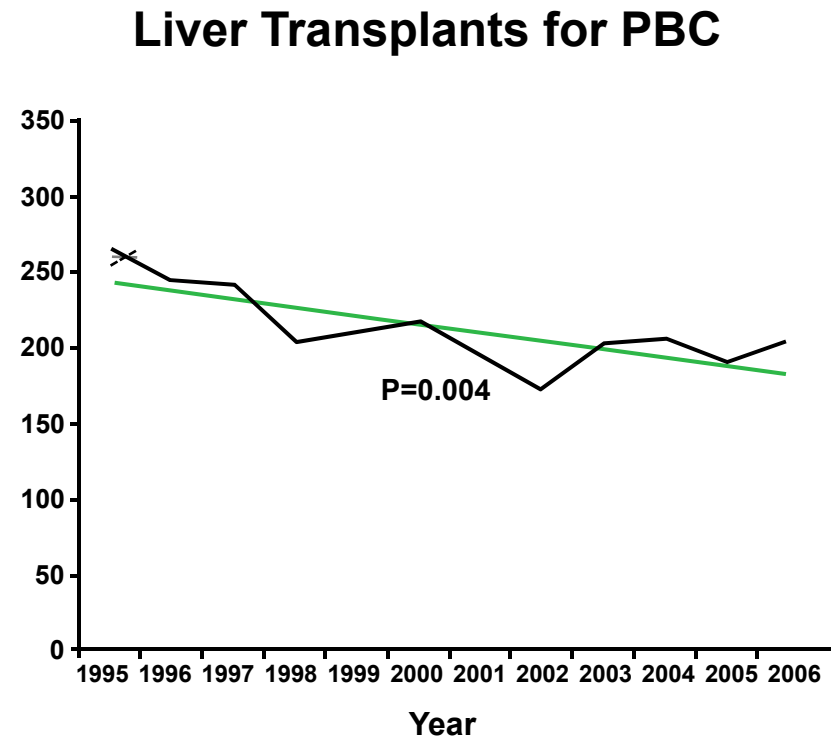
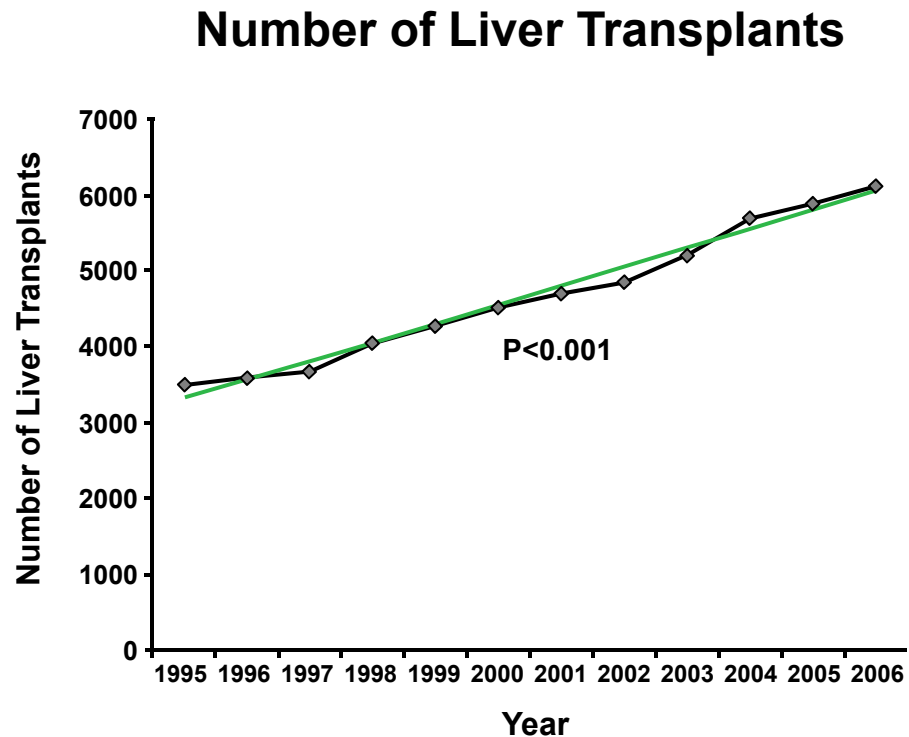
Prognostic index comprising baseline albumin and platelet count, plus bilirubin, ALT or AST, and ALP after 1 year UDCA

GLOBE Score³ (2015)

Prognostic index comprising baseline age, and bilirubin, ALP, albumin, and platelet count after 1 year UDCA

1. Trivedi PJ, et al. *J Hepatol.* 2014;60:1249-1258.
2. Carbone M, et al. *Hepatology.* 2016; 63(3): 697-99.
3. Lammers WJ, et al. *Gastroenterology.* 2015; 149(7):1804-12

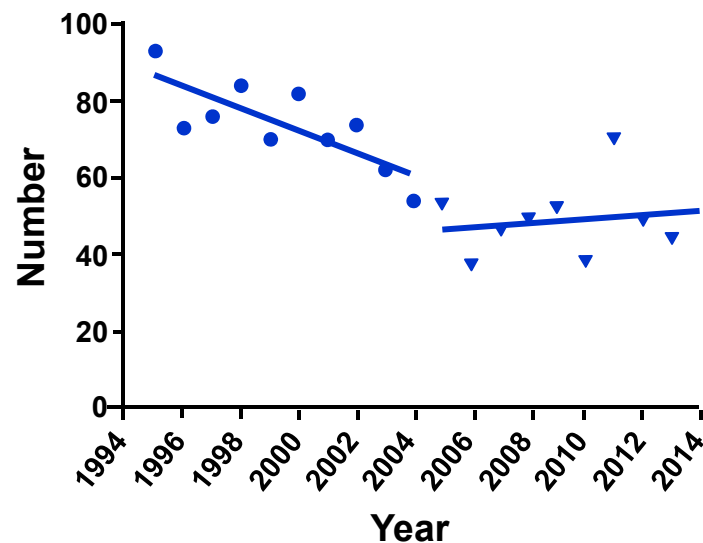
Liver Transplantation for PBC: Trends in the United States



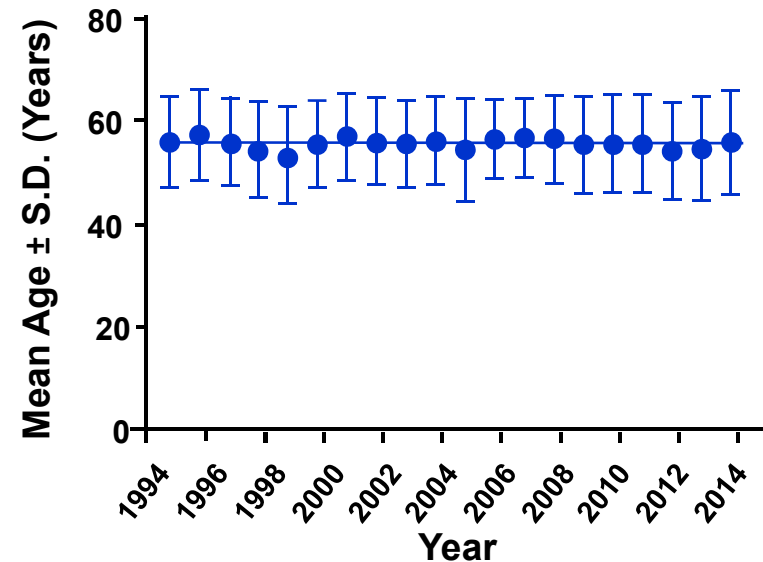
PBC Liver Transplant Data for the UK

Although liver transplants for PBC have decreased, the average age of patients with PBC undergoing liver transplant has not changed

Liver Transplants for PBC Performed/Year



Age at Transplantation



Summary and Conclusions

- **PBC is increasing in prevalence**
- **Substantial impact on quality of life**
- **May progress to end-stage liver disease, HCC**
- **Rates of progression are variable**
- **UDCA has been cornerstone of therapy,**
- **A substantial number of patients have a suboptimal response or intolerance to UDCA**

Introduction

Linda Robertson, PhD

*Intercept Pharmaceuticals, Inc.
Vice President, Regulatory Affairs
and Quality Assurance*

Obeticholic Acid for the Treatment of PBC

- Obeticholic Acid (OCA)
 - FXR agonist and modified bile acid
- PBC
 - Rare, chronic, serious non-viral liver disease
 - Life-threatening, leading to either death or liver transplantation
 - Limited therapeutic options
 - Ursodeoxycholic (UDCA) acid is the only approved therapy
 - Need for new therapies, particularly second line therapy

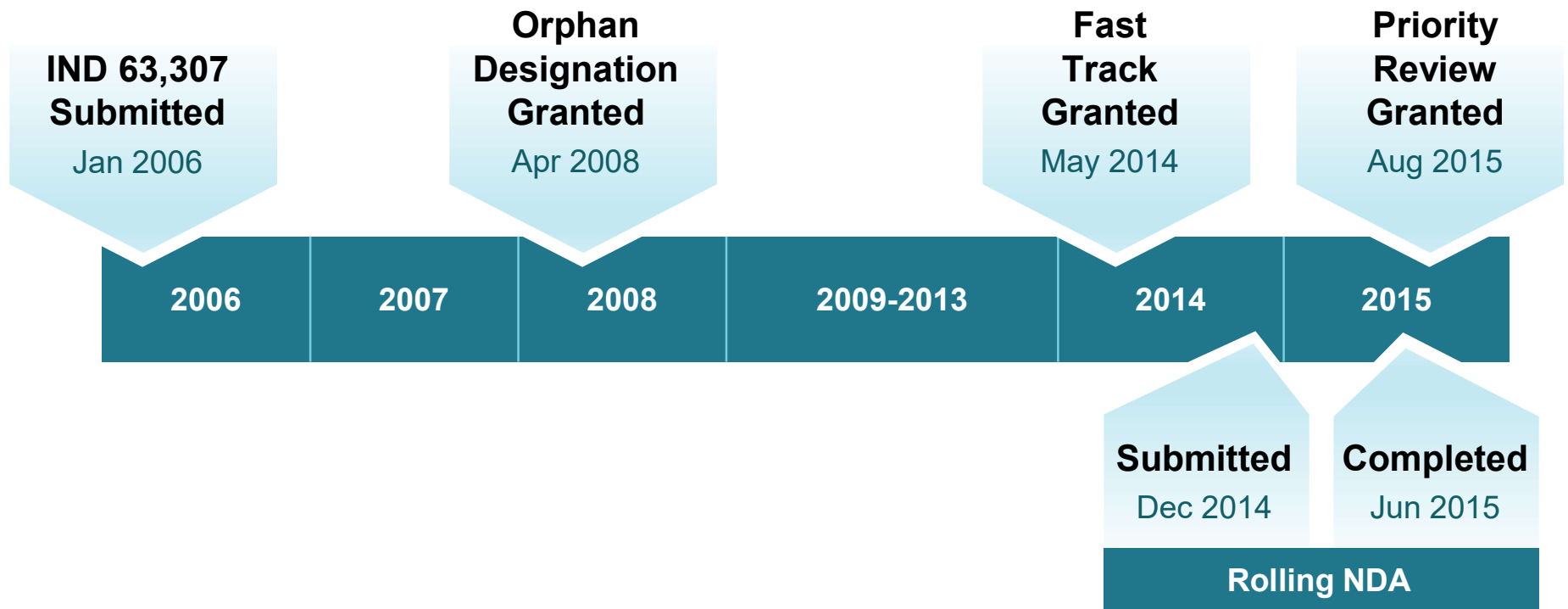
Regulatory Challenges in PBC

- Inherent challenges with regard to an approvable endpoint
- Chronic liver disease
 - Slow and variable rate of disease progression
 - Over 10 year median survival in patients with an inadequate response to UDCA
- Symptoms, i.e. pruritus and fatigue do not correlate with clinical outcomes
- Difficult to determine clinical benefit using conventional clinical outcomes in a timely fashion

Accelerated Approval

- Serious, life-threatening condition
- Meaningful advantage over existing therapies
- Surrogate endpoint “reasonably likely to predict clinical benefit”
 - Based on the entirety of clinical evidence including correlation with clinical outcomes and relationship to disease pathophysiology
- Requires confirmatory study underway at the time of filing to confirm clinical benefit

Regulatory History



Basis of Accelerated Approval

- One Phase 3 and two Phase 2 safety and efficacy double-blind studies with long-term safety extensions
- Statistically significant effects on composite biochemical endpoint
 - ALP change and maintenance of normal bilirubin
 - Shown to be associated with clinical outcomes based on data from independent study groups
- Over 1500 subjects exposed to OCA including ~400 patients with PBC for up to 5 years
 - Generally safe and well tolerated
- Ongoing Phase 4 confirmatory study
 - Initiated February 2015

Proposed Indication

Obeticholic Acid (OCA) is indicated for the treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA

Dosing and Administration

- Recommended starting dose is 5 mg once daily
- Based on the assessment of efficacy and tolerability after 3 months, the dose should be increased to 10 mg once daily to improve response

Agenda

Unmet Need in PBC

David Jones, MD FRCP, PhD

*Professor of Liver Immunology
University of Newcastle
Institute of Cellular Medicine
Director, UK-PBC Study Group Consortium*

Program Rationale

David Shapiro, MD FRCP

*Intercept Pharmaceuticals, Inc.
Chief Medical Officer*

Efficacy of OCA in PBC

Leigh MacConell, PhD

*Intercept Pharmaceuticals, Inc.
Vice President, Clinical Development*

Safety of OCA in Patients with PBC

Roya Hooshmand-Rad, MD, PhD

*Intercept Pharmaceuticals, Inc.
Executive Director, Medical Safety and Pharmacovigilance*

Benefit-Risk

John M. Vierling, MD FACP, FAASLD

*Baylor College of Medicine
Professor of Medicine and Surgery
Chief of Hepatology, Director of Advanced Liver Therapies*

Unmet Need in PBC

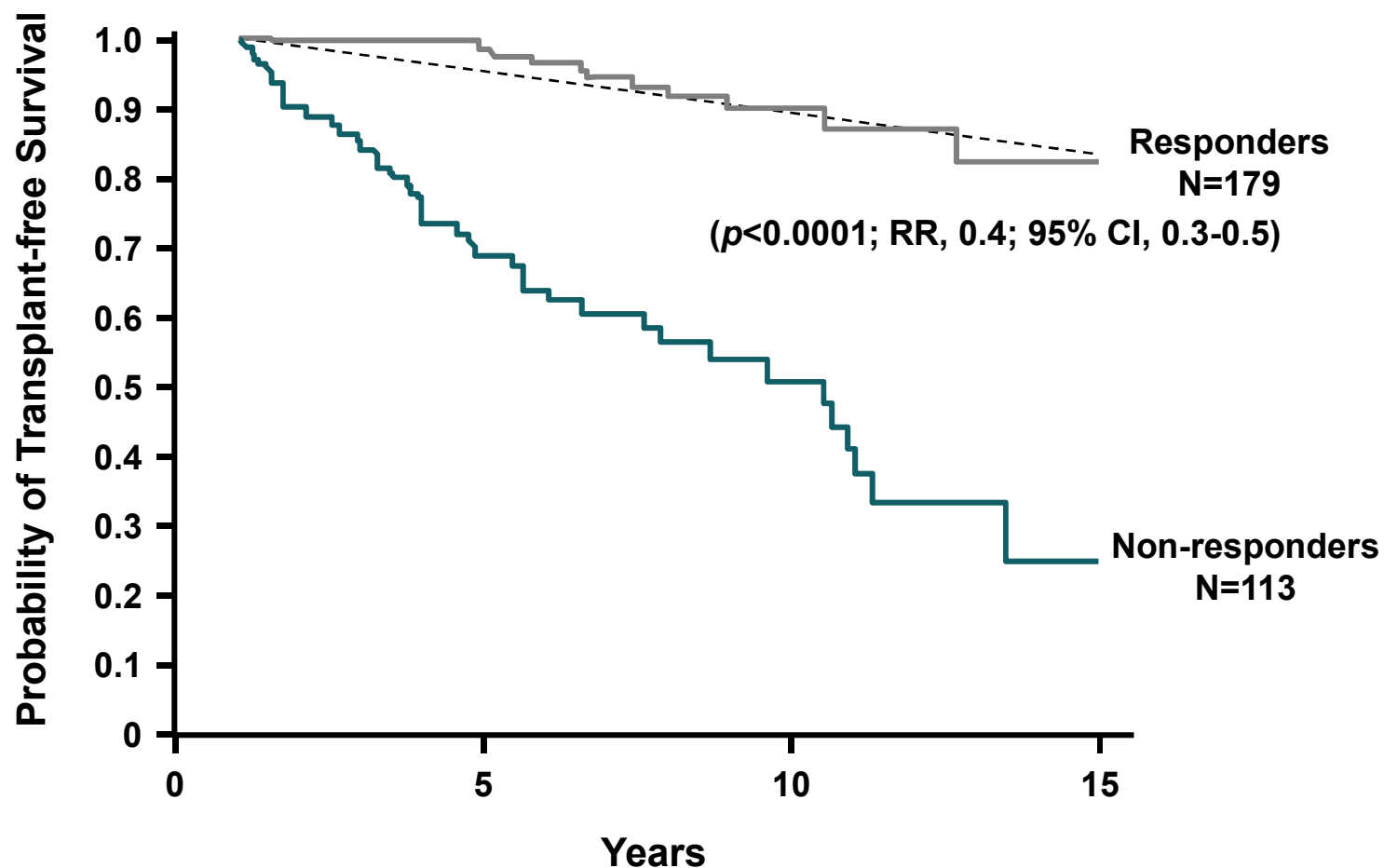
David Jones, MD FRCP, PhD

*Professor of Liver Immunology
University of Newcastle
Institute of Cellular Medicine
Director, UK-PBC Study Group Consortium*

Limitations of Current Management

- UDCA
 - Up to 40% of patients unresponsive to therapy
 - Additional 5% are intolerant to therapy
- Transplantation
 - Cost
 - Morbidity
 - Poor functional status
 - Limited timely organ availability and differential access
- Clinical trials
 - Rare disease – requires large number of centers for studies
 - Relatively slow progression of disease
 - Precludes easy evaluation of clinical outcomes as primary endpoint

Biochemical Response to UDCA at 1 Year Predicts Disease Progression



Global PBC Study Group

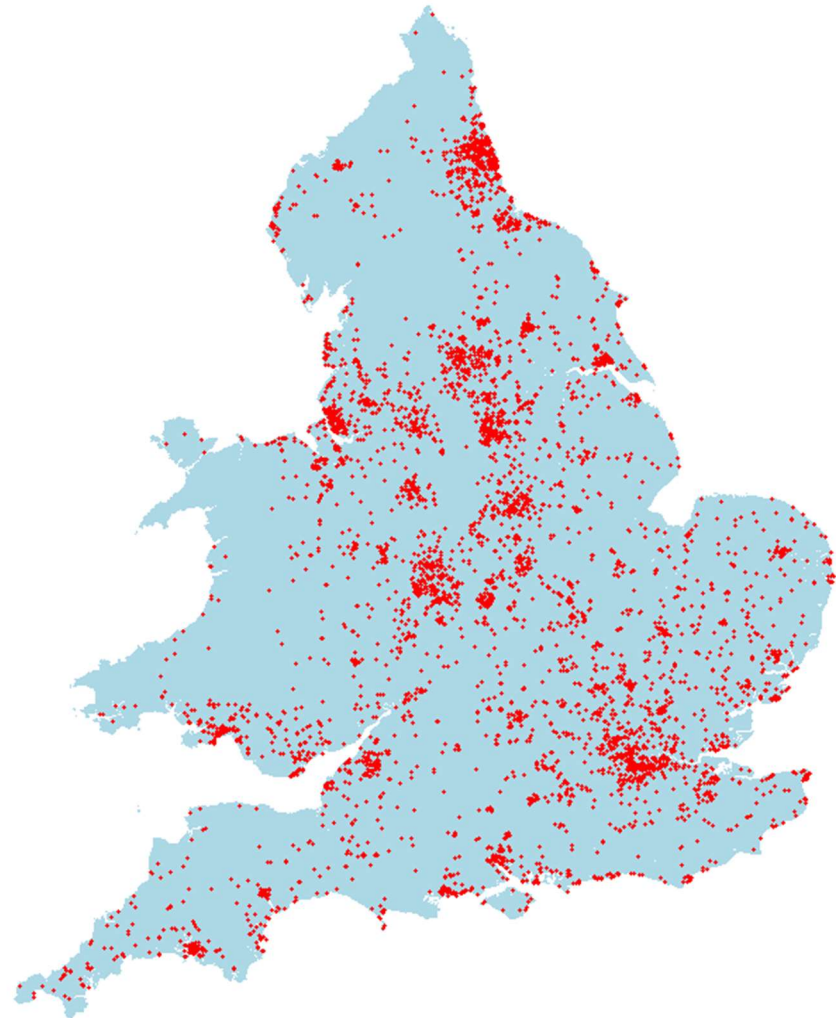
- Global PBC Study Group, an international and multicenter collaboration between 15 liver centers in 8 North American and European countries
- Combined individual patient data from major long-term follow-up cohorts
- Clinical data of 6191 PBC patients



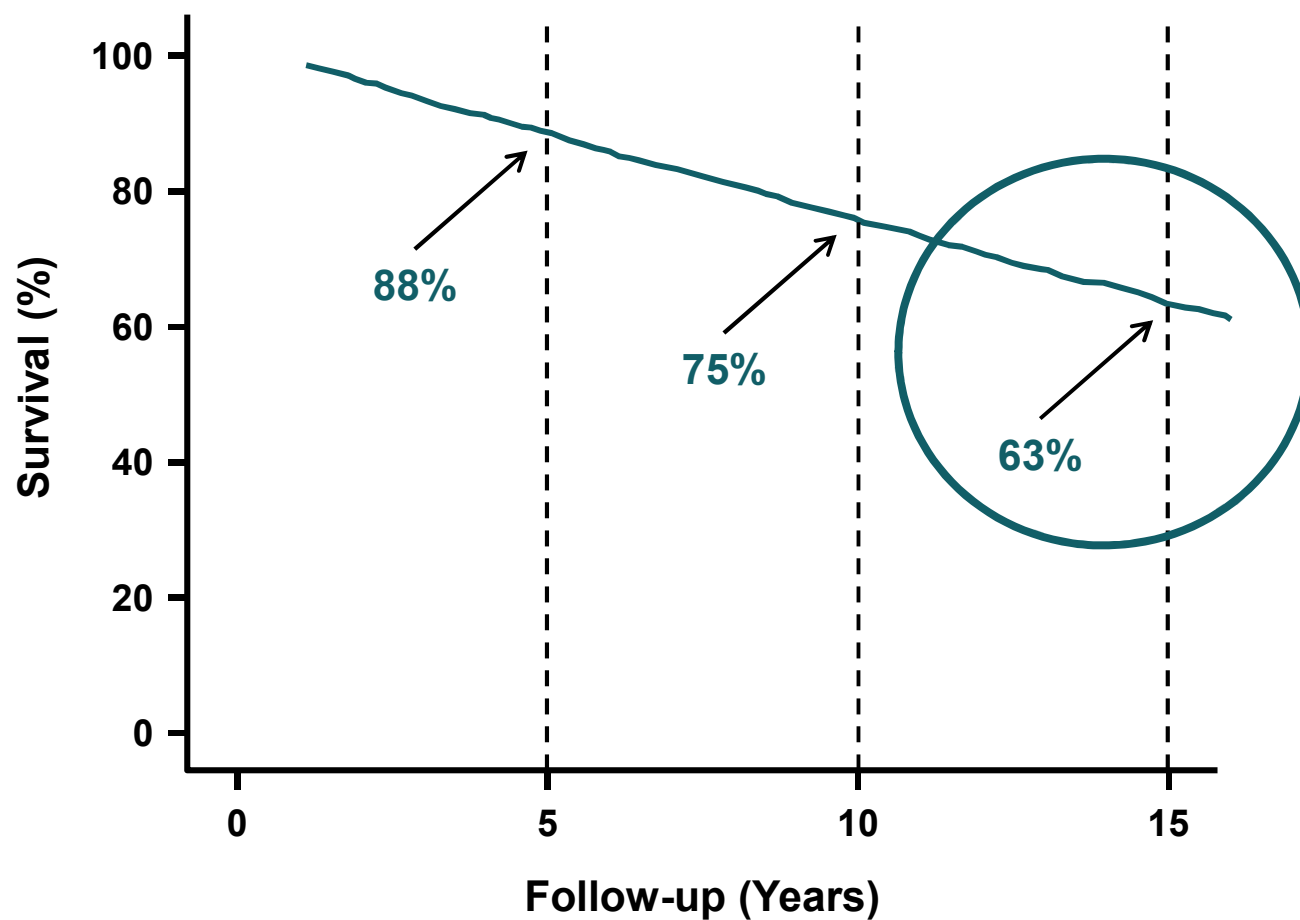
Lindor KD, et al. Hepatology. 2009;50:291-308; 2. European Association for the Study of the Liver. J Hepatol. 2009;51:237-267; Lammers, WJ et al. Gastroenterology. 2014 Dec;147(6):1338-1349.

UK-PBC Consortium

- Meta-analysis of individual patient data
- Long-term follow-up cohorts from 150 National Health Service Trusts or Health Boards
- 100% of UK hospitals and ~35% of UK patients
- Clinical data of >6000 PBC patients



Unmet Need: Transplant-Free Survival in UDCA Era

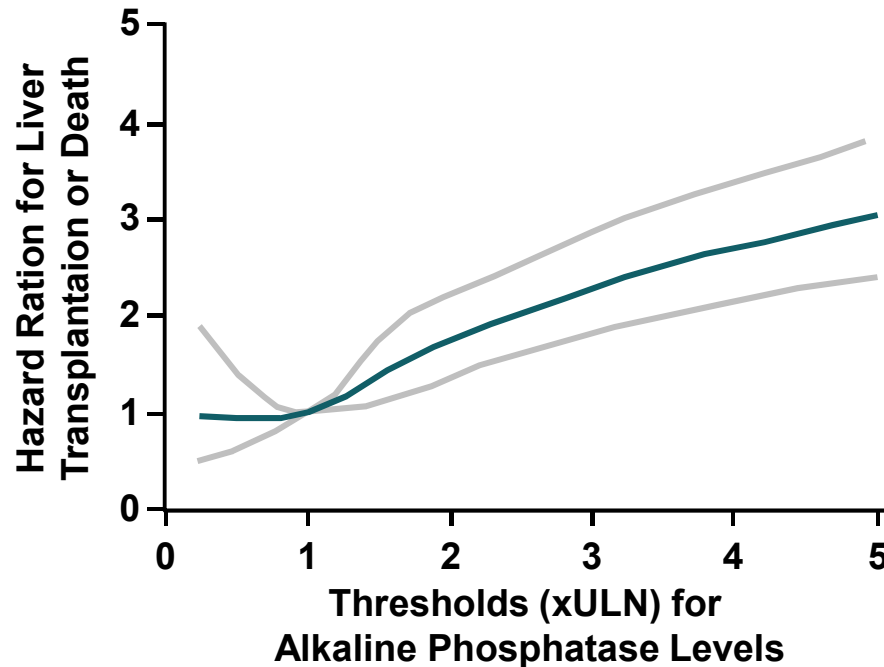


Adapted from Lammers et al. Gastroenterology. 2014; 147(6):1338-49

Elevated ALP and Bilirubin Values are Associated With Higher Hazard of Liver Transplantation/Death

Alkaline Phosphatase (ALP)

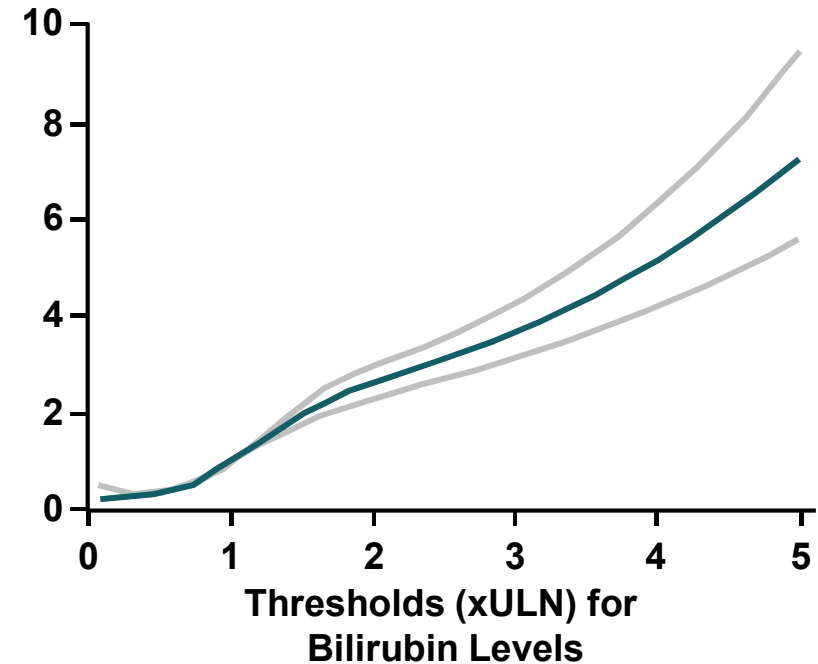
At one year follow-up*



*3710/4635 patients were included for this analysis

Bilirubin

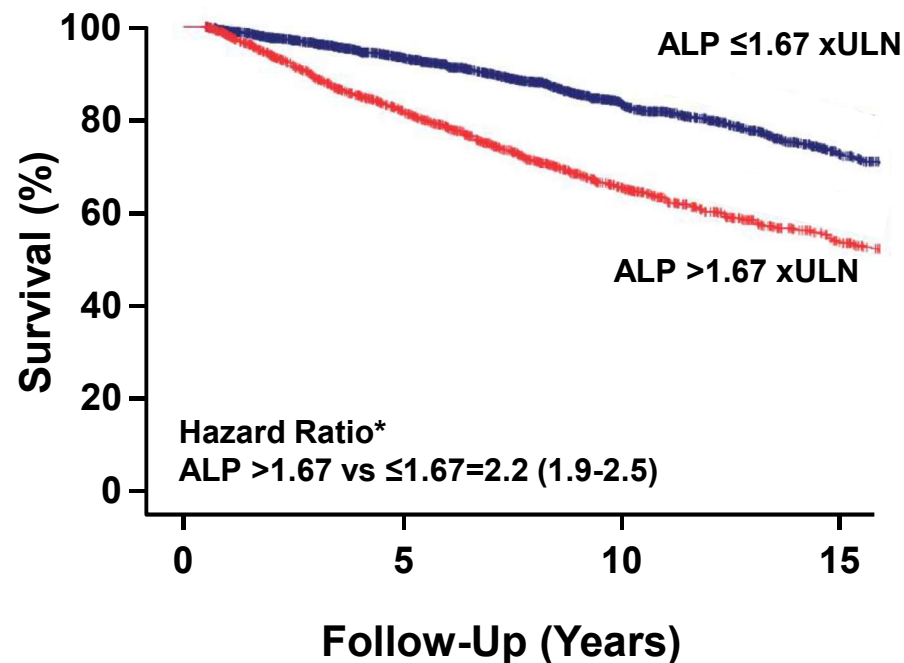
At one year follow-up*



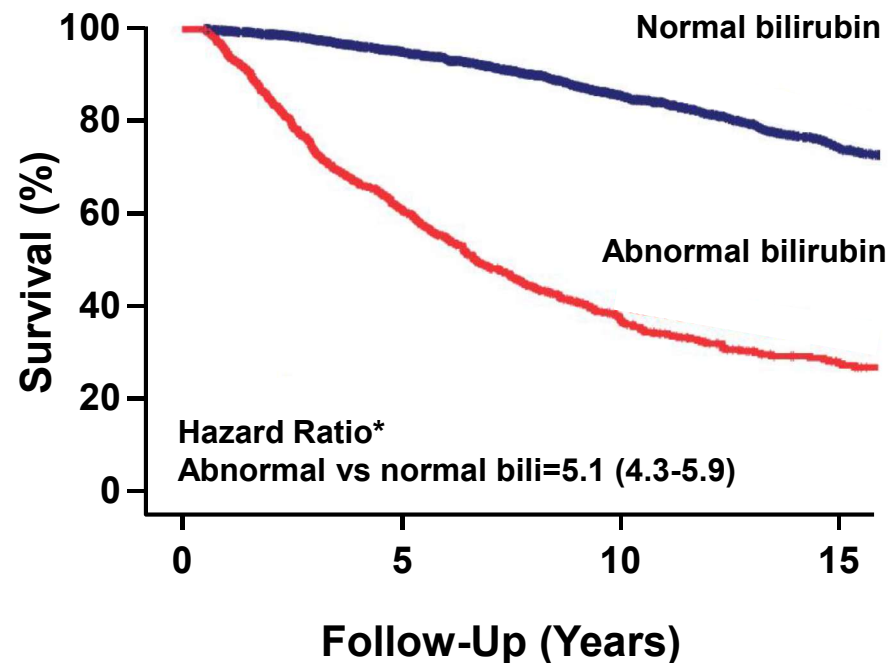
*3681/4635 patients were included for this analysis

Dichotomous ALP and Bilirubin Classifiers Predict Survival

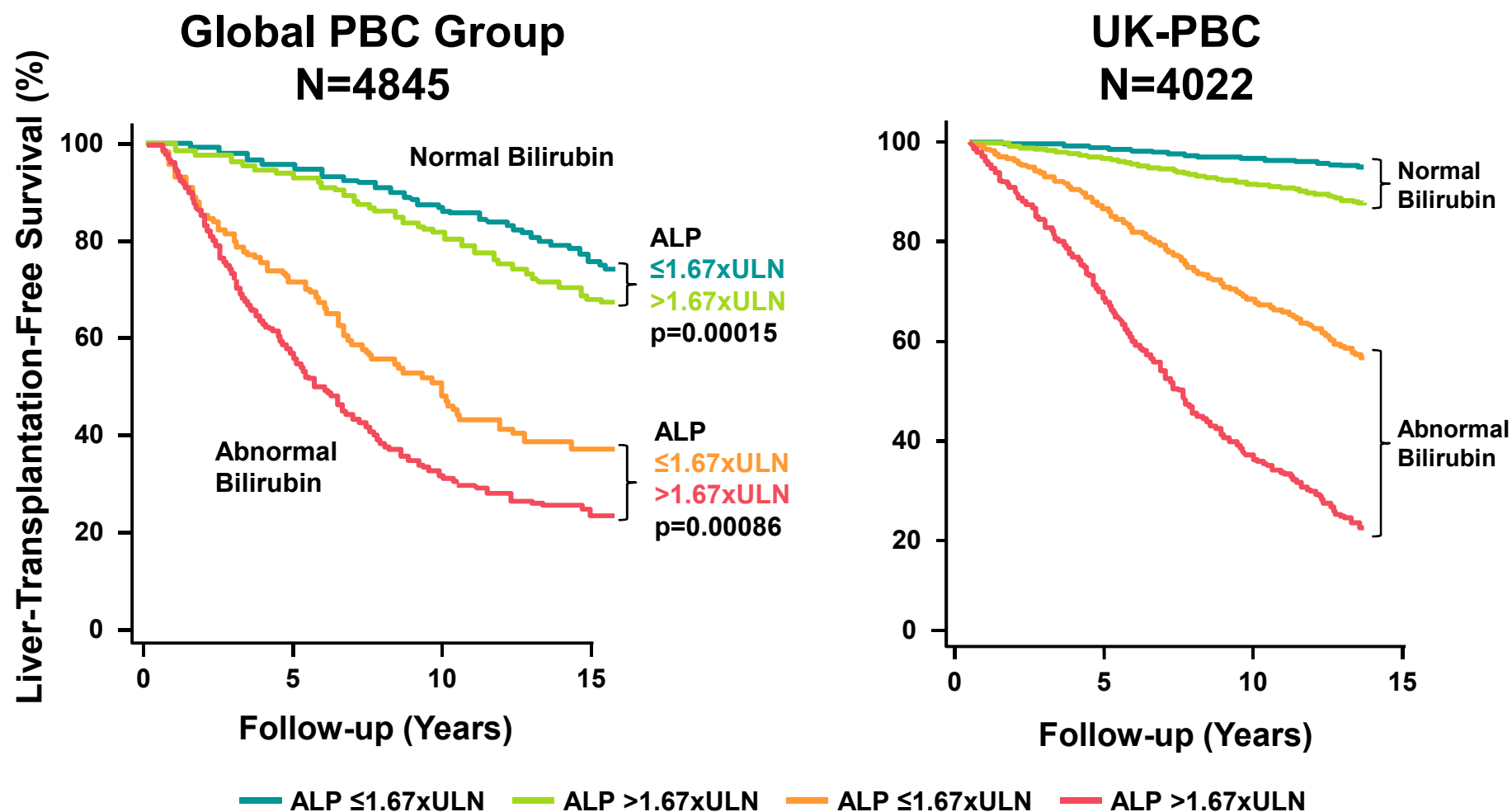
Alkaline Phosphatase (ALP)



Bilirubin

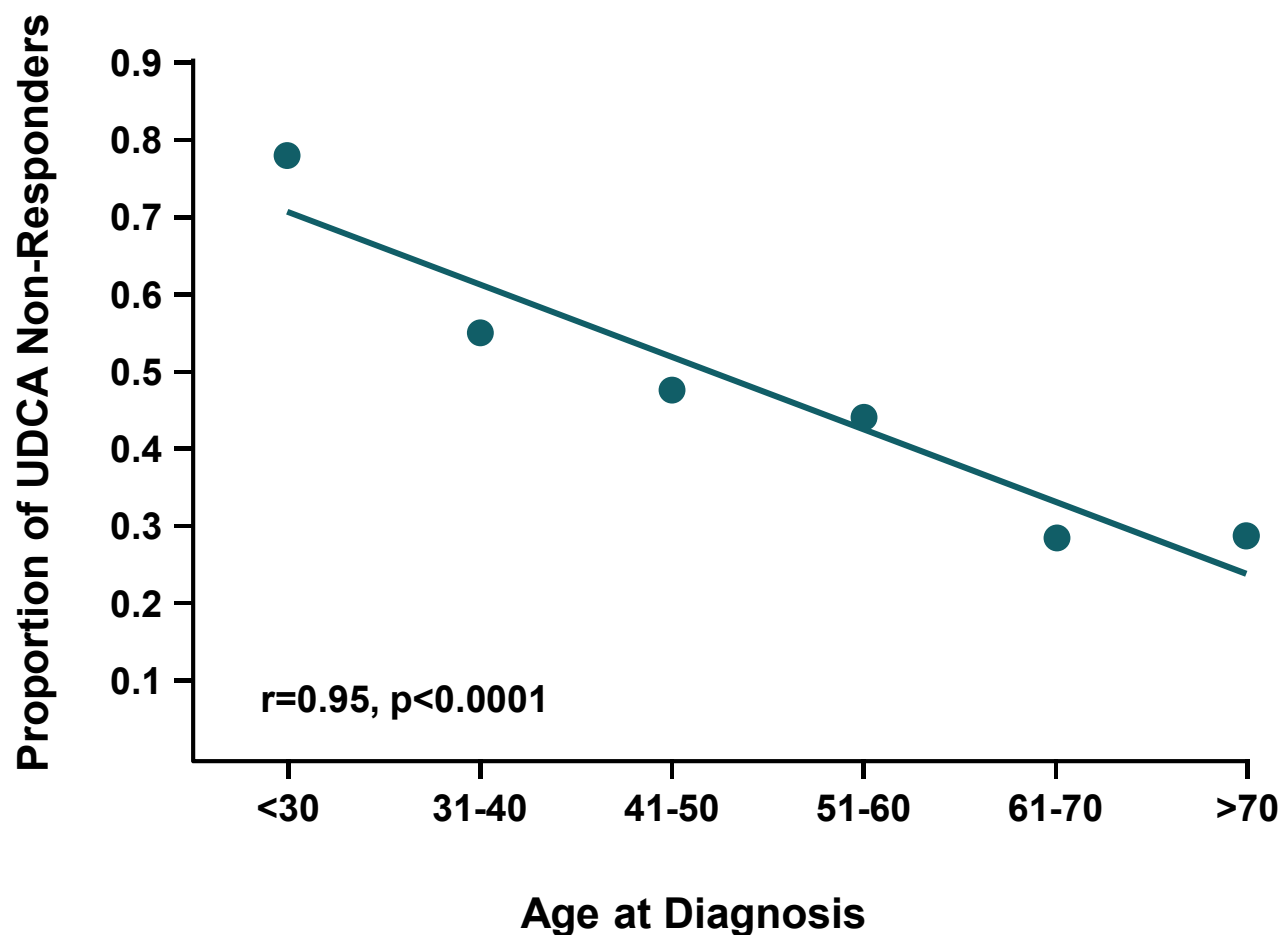


ALP Values Have Predictive Significance in Addition to Bilirubin in Patients with PBC



Liver transplant-free survival for Global PBC is based on all-cause mortality or liver transplant and the UKPBC is based on liver-related death or liver transplant. Courtesy of Global PBC Study Group and UK-PBC

Greatest Risk of Non-Response Associated With Younger Age at Diagnosis



Carbone et al. Gastroenterology. 2013; 144(3): 560-69.

Management of PBC in the UDCA Era

- UDCA universally used
- Routine assessment after 1 year of treatment
- Capacity to identify minority of patients in whom death liver transplant risk resides (low risk patients in whom therapy can be stepped down)
- Capacity to target early in the disease course high efficacy therapies in high risk patients (risk vs stage)
- **Trial measures to assess response to therapy**

Vision for the Future of PBC Management

- Better treatment targeted in better ways
- Key attributes of new therapies include
 1. Targeted for patients with unmet need through appropriate risk stratification
 2. Proof of benefit in studies of appropriate patient cohorts
 3. Manageable and tolerable side effects

Program Rationale

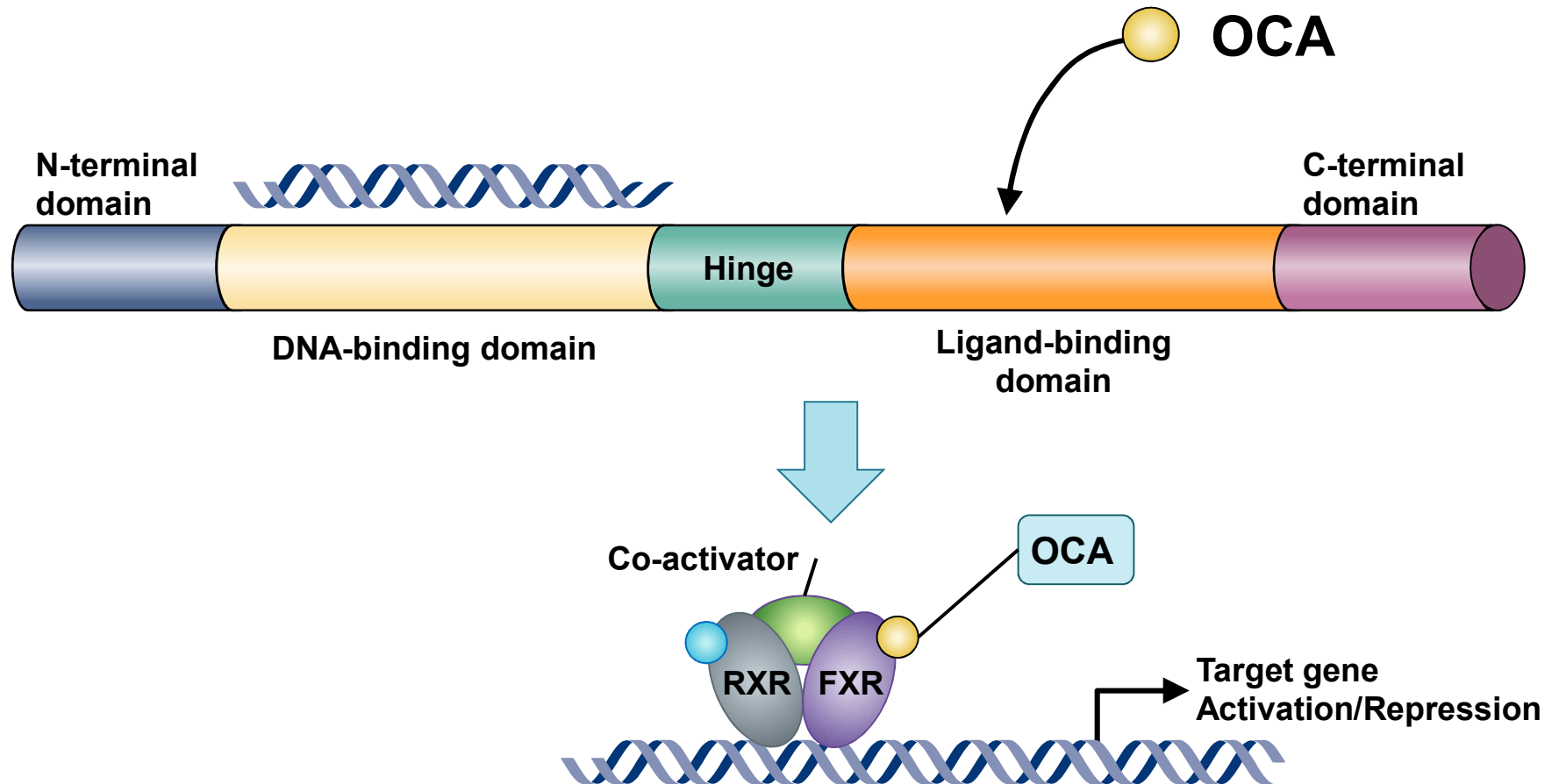
David Shapiro, MD FRCP

Intercept Pharmaceuticals, Inc.
Chief Medical Officer

Goals for a New PBC Therapeutic

- Drug with desirable pharmacology
 - Increase bile flow – “choleresis”
 - Decrease toxic endogenous bile acid concentrations in hepatocytes
 - Lessen hepatobiliary inflammation and injury
- Farnesoid X Receptor – good therapeutic target
 - Regulates bile acid homeostasis
 - Pleotropic hepatic properties

FXR Activation

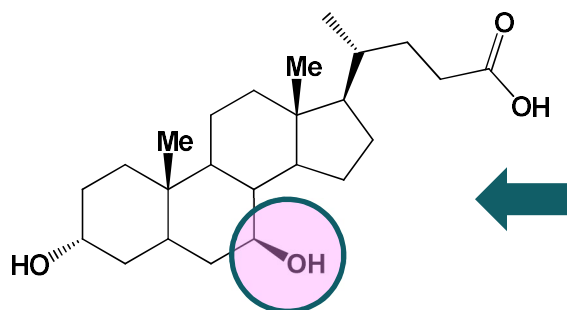


Obeticholic Acid (OCA)

6 α -ethyl chenodeoxycholic acid

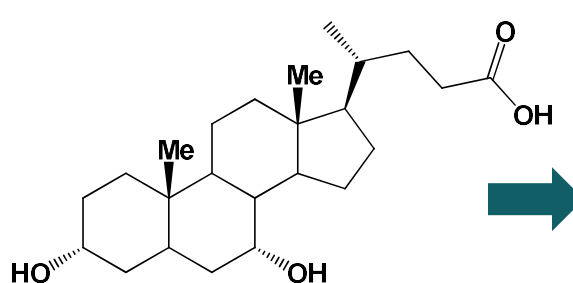
UDCA

Ursodeoxycholic Acid



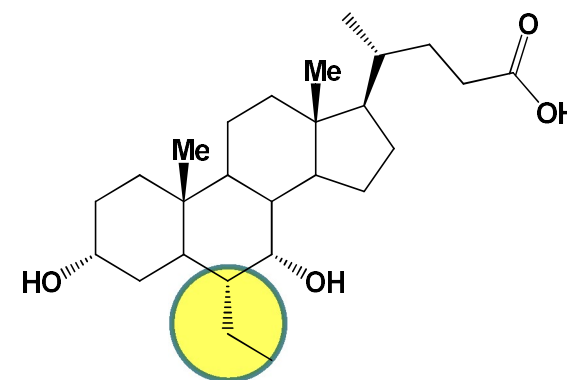
CDCA

Chenodeoxycholic Acid



OCA

6 α -ethyl chenodeoxycholic acid



**FXR EC₅₀
(agonist)**

No activity

8.66 μ M

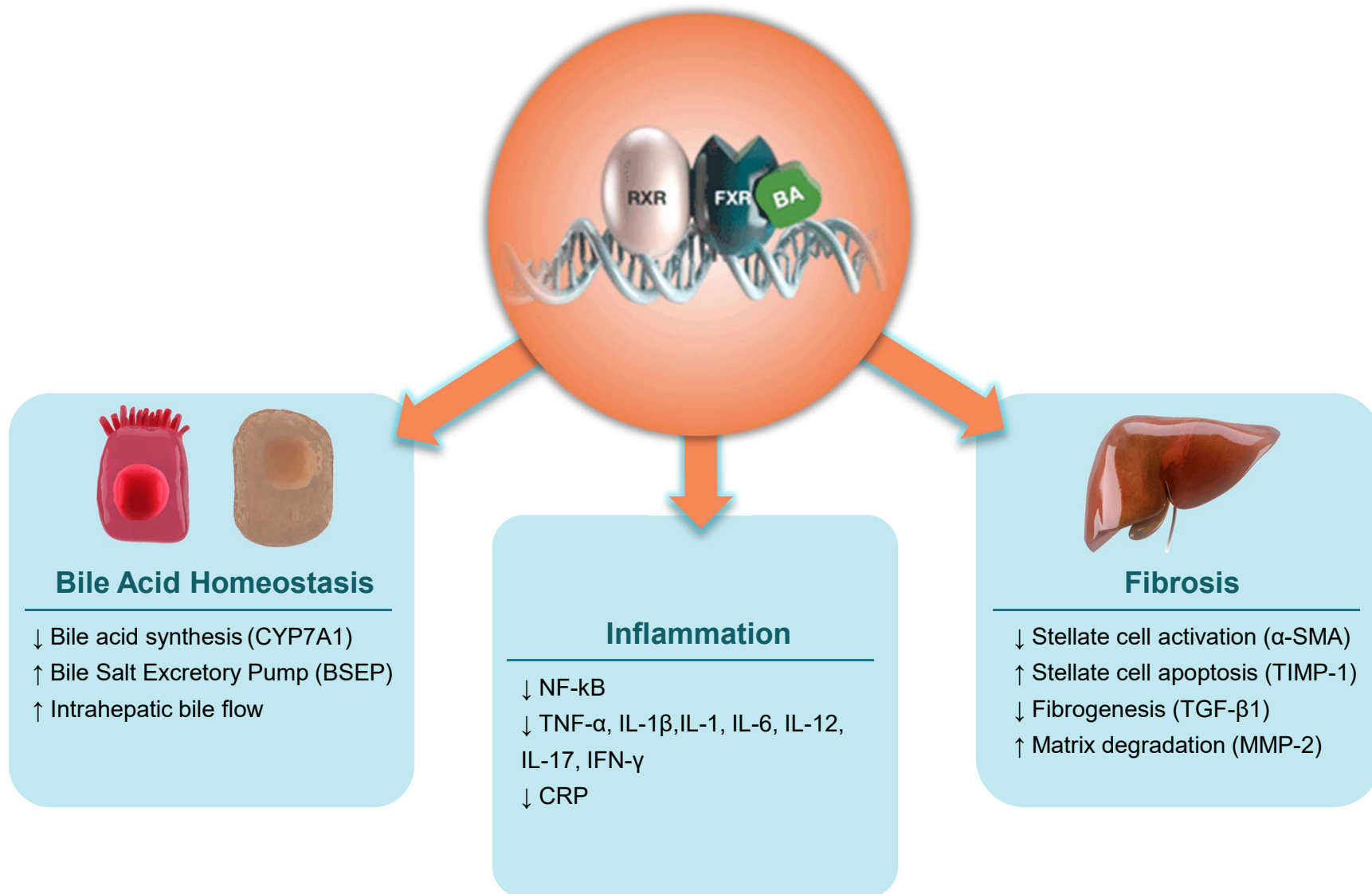
0.099 μ M

~100x \uparrow FXR agonism

OCA – Key Properties

- Pharmacokinetic properties similar to endogenous CDCA
 - Selective FXR agonist
 - No binding to other nuclear receptors
 - Rapidly absorbed
 - Metabolism: conjugation with glycine and taurine
 - Equipotent FXR agonists to parent OCA
 - Extensive enterohepatic re-circulation
 - Steady-state half life: ~4 days
 - Excretion
 - Fecal >85%
 - Urine <3%

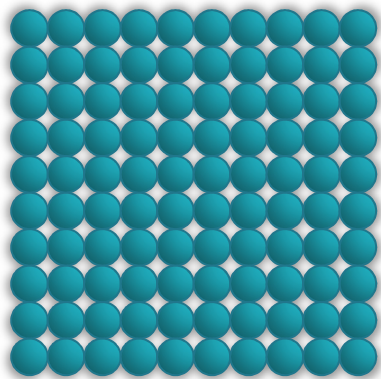
FXR-Mediated Pharmacological Actions of OCA



UDCA and OCA Properties

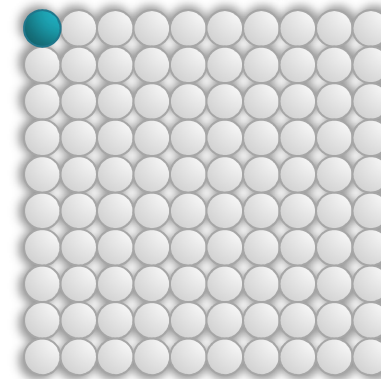
UDCA

~1000 mg



OCA

5→10 mg



No FXR activation

Post-transcriptional

No change in BA synthesis but $\uparrow\uparrow$ BA pool

Major circulating BA & \uparrow hydrophilicity of BA pool

Stimulation of biliary HCO_3^- \rightarrow biliary epithelium protection

Potent FXR activation

Transcription effects

BA synthesis \downarrow

$<2\%$ of BA pool

\uparrow choleresis (bile flow)
 \downarrow inflammation and fibrosis

Clinical Program Overview: >20 Studies

- 1500 subjects
- PBC: ~430 patients, ~675 patient years exposure
- Biopharmaceutics – 4 studies
 - Bioavailability and bioequivalence
- Clinical Pharmacology – 12 studies
 - Food effect
 - Drug-Drug Interactions – 5 studies, multiple probes
 - Thorough QTc – CV safety
- Other potential indications
- Primary Biliary Cirrhosis/Cholangitis – 3 studies
 - 2 Phase 2 studies
 - 1 Phase 3 study

Efficacy of OCA in PBC

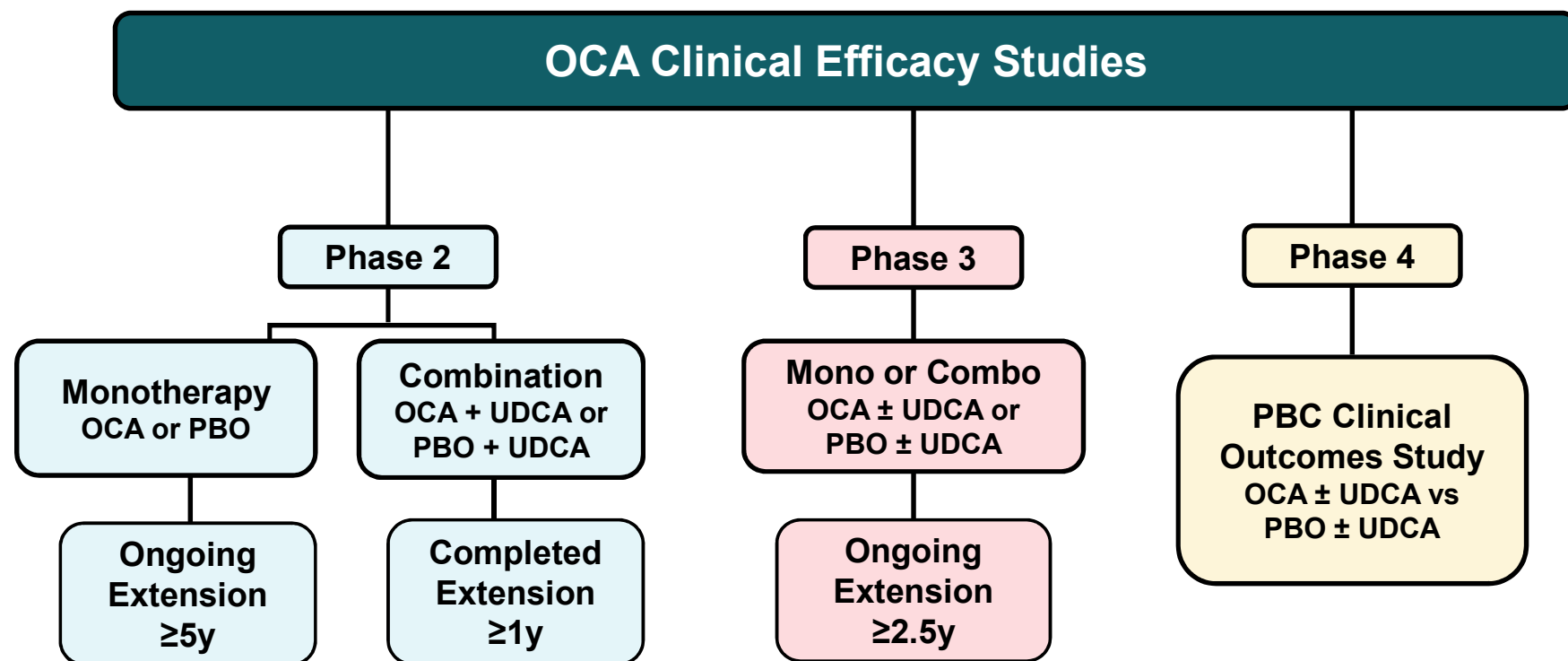
Leigh MacConell, PhD

Intercept Pharmaceuticals, Inc.

Vice President

Clinical Development

Randomized Placebo-controlled Studies With Primary Efficacy Data in Patients with PBC



**Two observational (retrospective and prospective) PBC databases
>10,000 Patients**

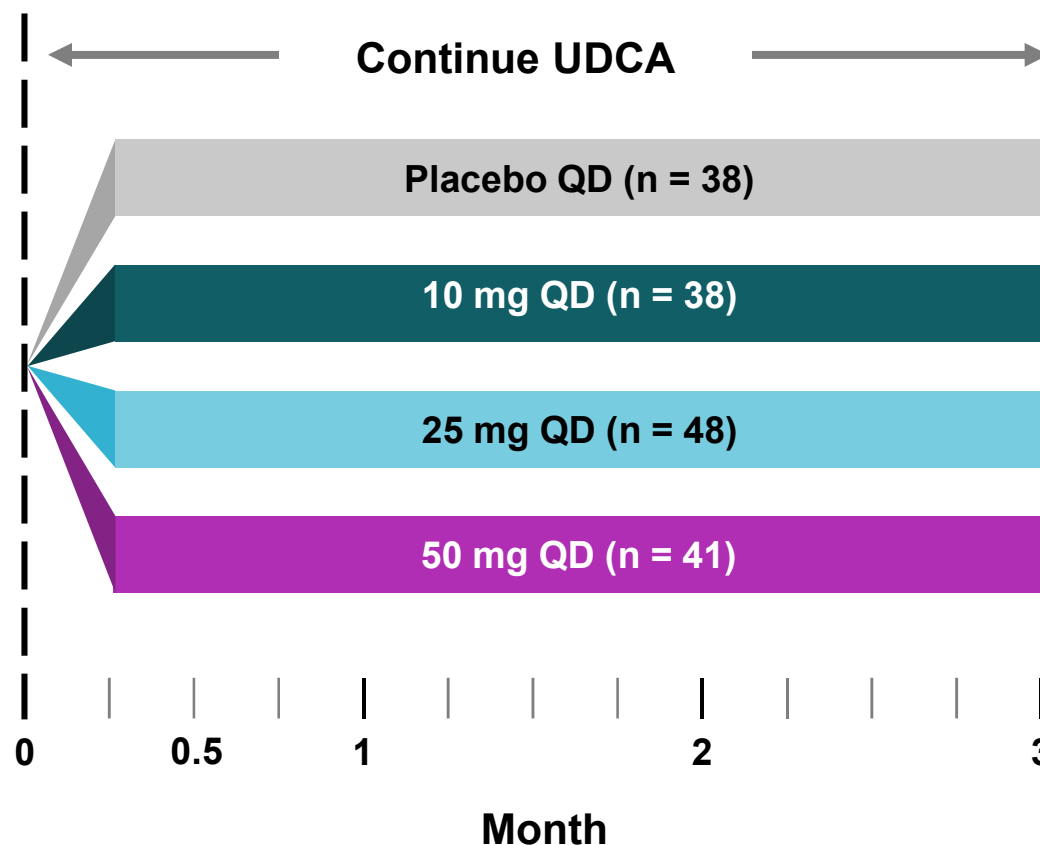
Proof of Concept – OCA as Add-On to UDCA

Double-Blind Phase 2

3-Month Double-Blind Treatment Period (ITT Population, N = 165)

Entry Criteria

- Diagnosis of PBC
- ALP 1.5x to 10x ULN
- Conjugated Bili ≤ 2 x ULN
- No prior history of hepatic decompensation
- Stable UDCA ≥ 6 Months

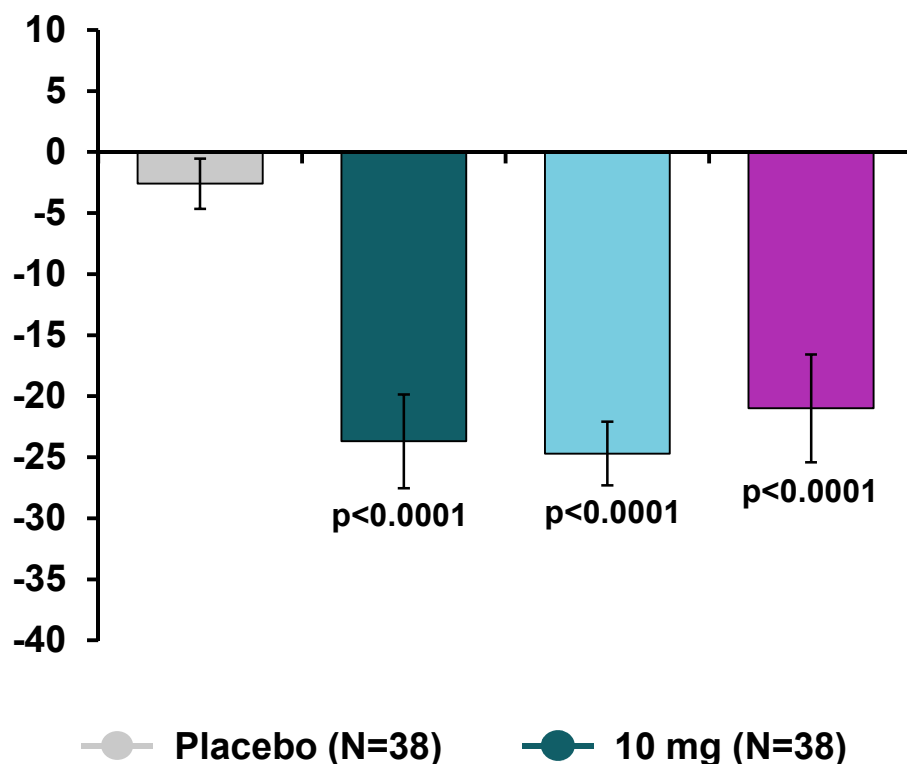


OCA Effective in PBC Patients Treated With UDCA

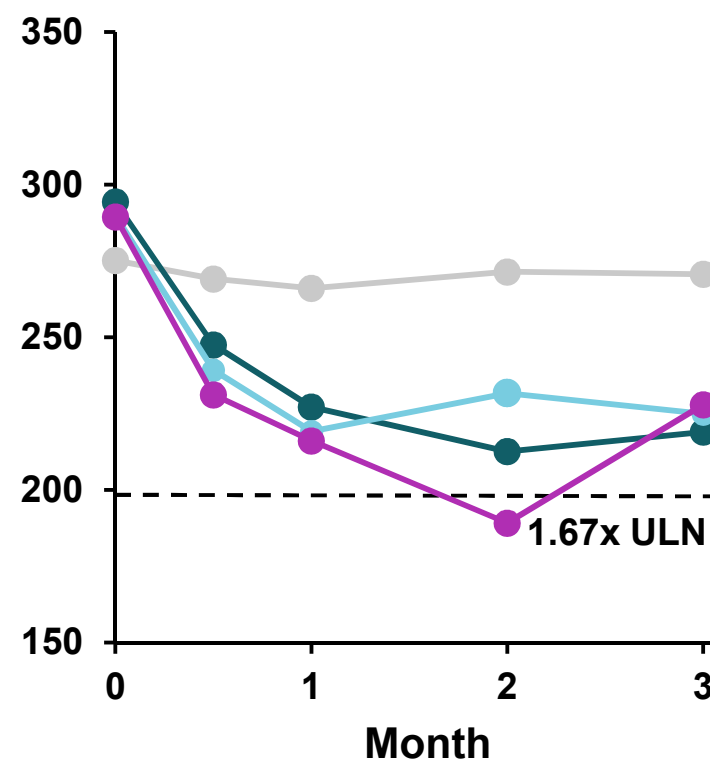
Double-Blind Phase 2 – Add on to UDCA

Primary Endpoint

Percent Change in ALP (U/L) From Baseline to Month 3



Mean ALP (U/L) Over Time



The primary efficacy endpoint was analyzed using the 2-sided Wilcoxon-Mann-Whitney test.

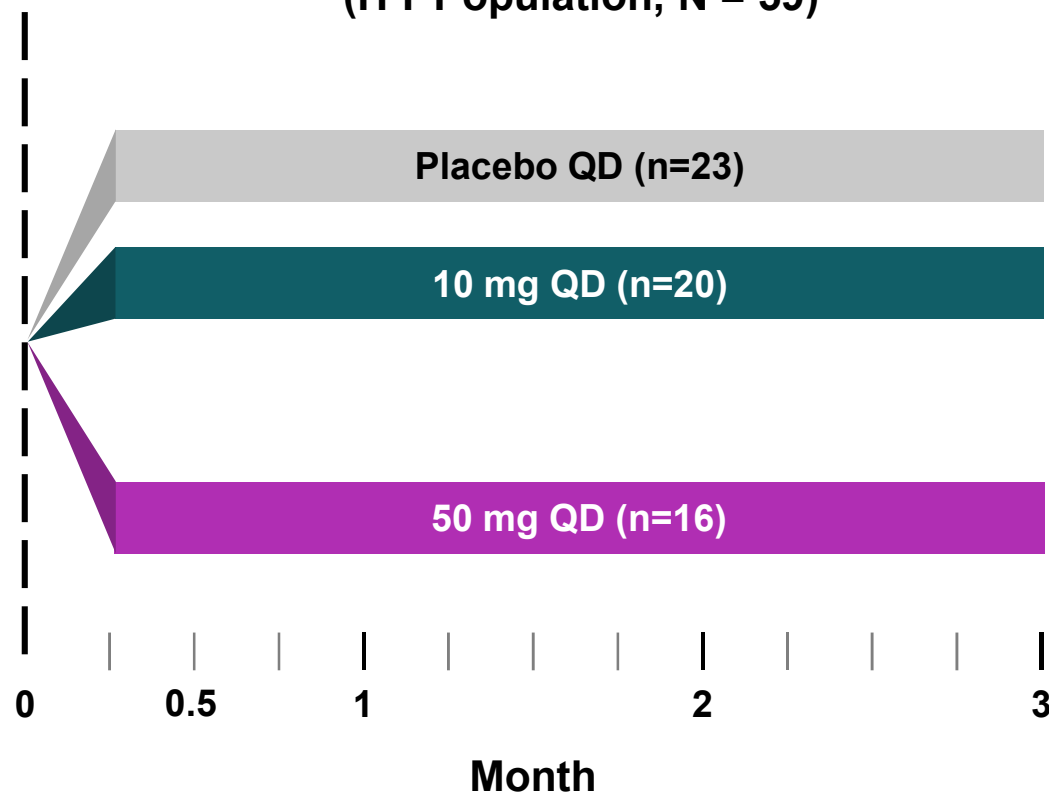
Proof of Concept – OCA Monotherapy

Double-Blind Phase 2

Key Entry Criteria

- Diagnosis of PBC
- ALP 1.5x to 10x ULN
- Conjugated Bili ≤ 2 x ULN
- No prior history of hepatic decompensation
- No UDCA ≥ 3 Months

3-Month Double-Blind Treatment Period (ITT Population, N = 59)

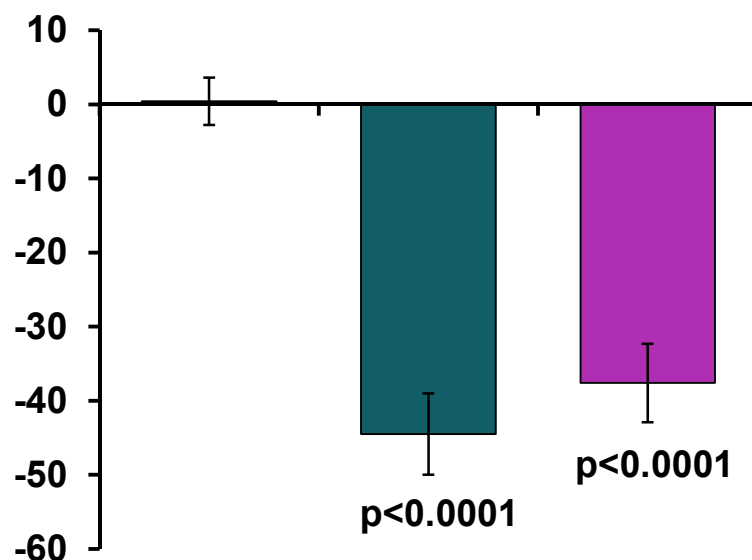


OCA Effective as Monotherapy

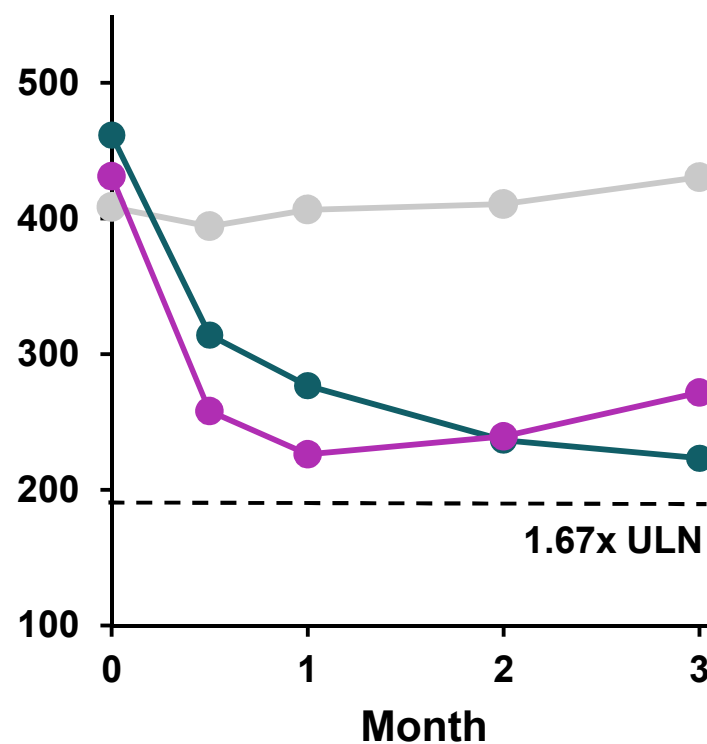
Double-Blind Phase 2 – Monotherapy

Primary Endpoint

Percent Change in ALP (U/L) From Baseline to Month 3



Mean ALP (U/L) Over Time



● Placebo (N=23) ● 10 mg (N=20) ● 50 mg (N=16)

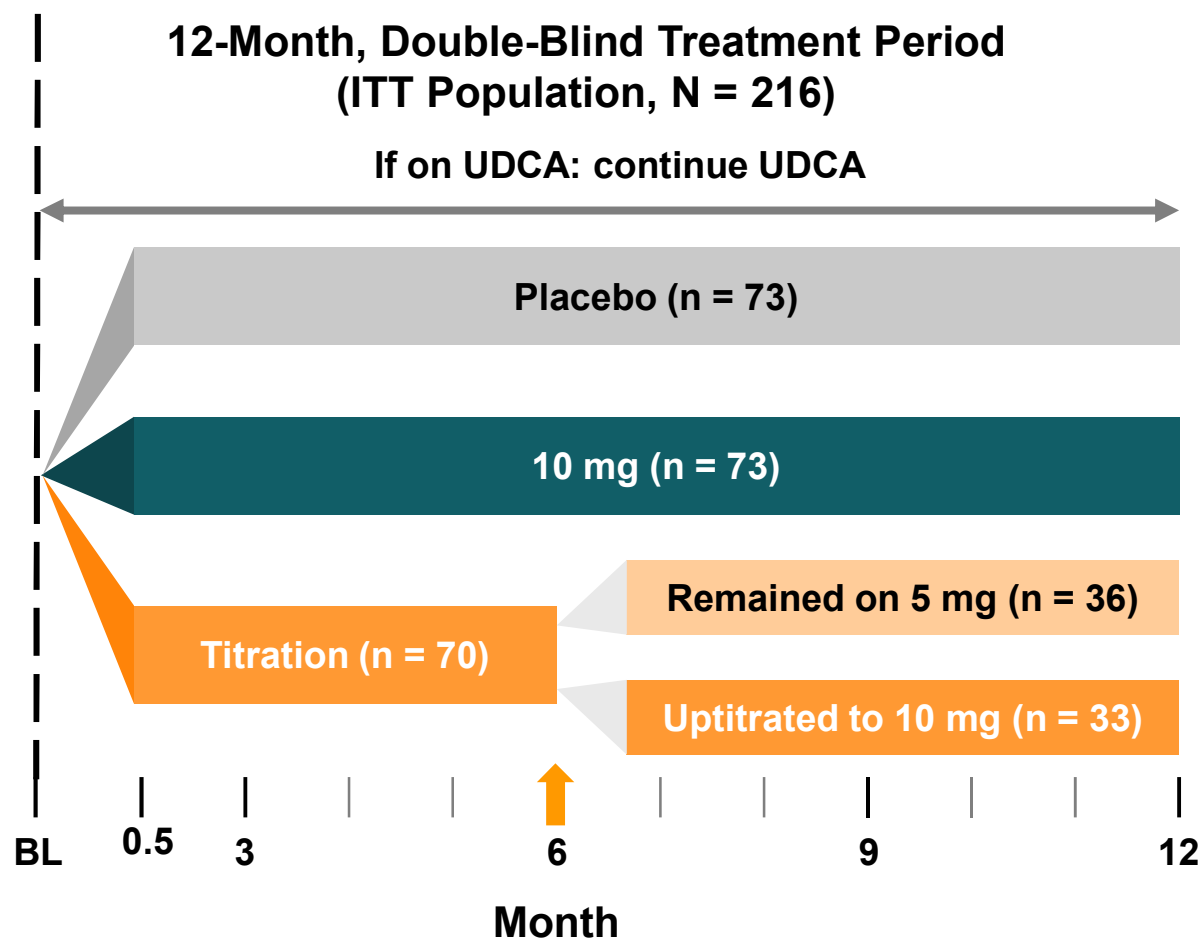
The primary efficacy endpoint was analyzed using the 2-sided Wilcoxon-Mann-Whitney test.

Pivotal Trial – OCA Evaluated in High Risk PBC Patients

Double-Blind Phase 3

Entry Criteria

- PBC diagnosis
- UDCA for at least 12 months (*stable dose for ≥ 3 months*)
- or
- Unable to tolerate UDCA (*no UDCA for ≥ 3 months*)
- ALP $\geq 1.67 \times$ ULN **or** Total bilirubin between $>ULN$ and $<2 \times$ ULN
- Presence of hepatic decompensation



↑ In the titration arm, patients **were to up-titrate from 5 mg to the 10 mg dose** if they had not yet achieved the primary composite endpoint and were tolerating therapy.

Primary Endpoint

Double-Blind Phase 3

- Proportion of patients achieving ALP $<1.67\times$ ULN
- **and**
- ALP decrease of $\geq 15\%$
- **and**
- Total Bilirubin \leq ULN

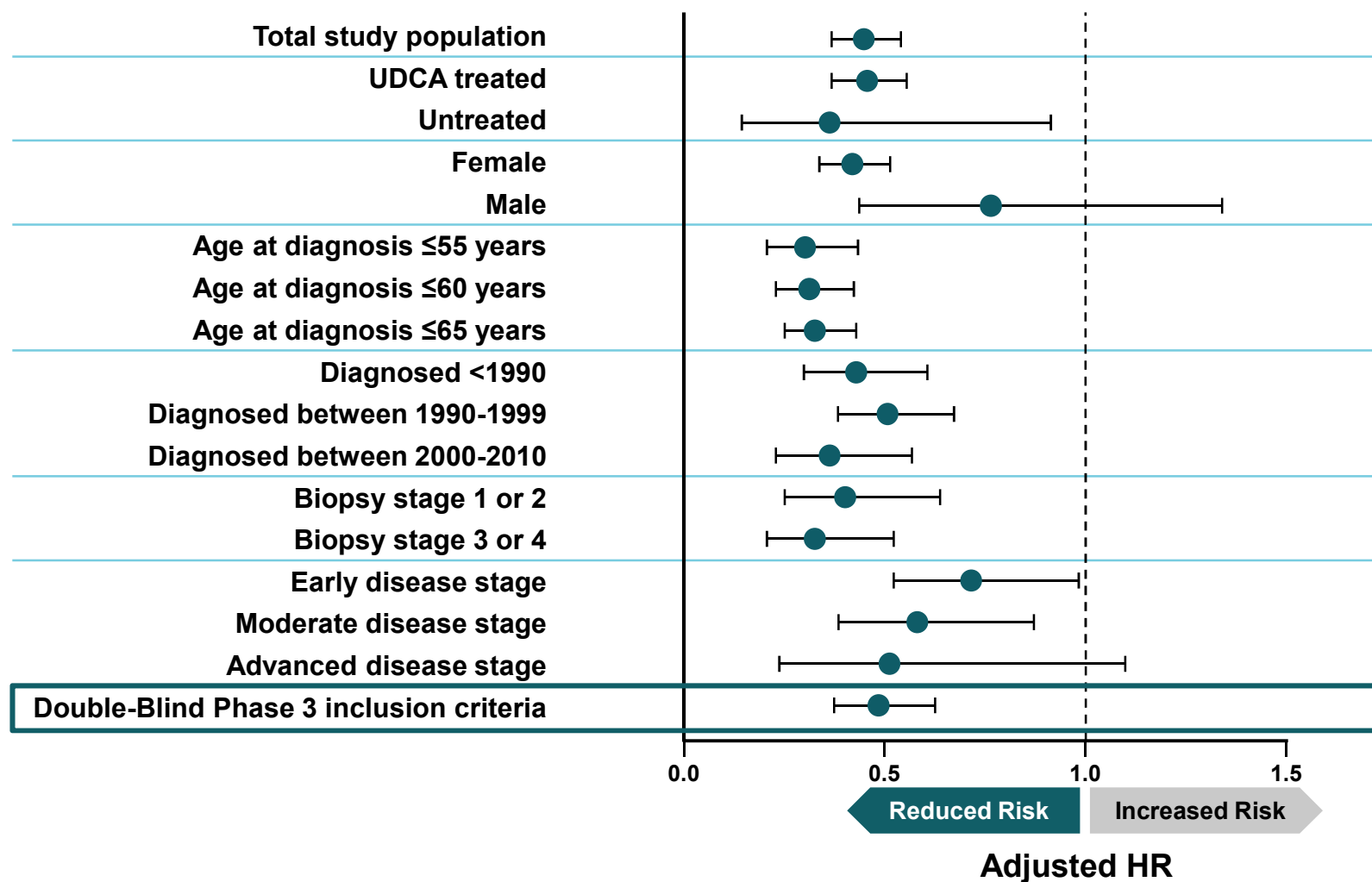
Endpoints of ALP and Bilirubin:

- ALP is a marker of cholestasis used for diagnosis and management of PBC
- Bilirubin is an established marker of hepatic excretory function
- Both ALP and Bilirubin are established as independent predictors of risk in PBC
- Additive predictive utility when used together

Prognostic Utility of Primary Endpoint

Global PBC Database

ALP <1.67xULN with 15% Reduction from Baseline
and Normal Bilirubin at 1 Year of Follow-up



Secondary Endpoints

Double-Blind Phase 3

Secondary Endpoints	Markers of Disease Progression
ALP and GGT	Cholestatic injury
Bilirubin	Loss of excretory function
ALT and AST	Hepatocellular injury
IgM	Immunological abnormalities
hs-CRP	Systemic inflammation

Patient Analysis Populations

Double-Blind Phase 3

	Placebo n (%)	Titration n (%)	10 mg n (%)	Total n (%)
Enrolled/randomized	73	71	73	217
ITT population	73 (100)	70 (99)	73 (100)	216 (99.5)
Safety population	73 (100)	70 (99)	73 (100)	216 (99.5)
Completed DB phase	70 (96)	64 (90)	64 (88)	198 (91)

Demographics

Double-Blind Phase 3

	Placebo N=73	Titration N=70	10 mg N=73	Total N=216
Characteristic				
Caucasian, n (%)	66 (90)	67 (96)	70 (96)	203 (94)
Female, n (%)	68 (93)	65 (93)	63 (86)	196 (91)
Age (years), mean \pm SD	56 \pm 10	56 \pm 11	56 \pm 11	56 \pm 10
≥ 65 years, n (%)	13 (18)	10 (14)	17 (23)	40 (19)

Baseline Characteristics Reflective of High Risk PBC Population Double-Blind Phase 3

	Placebo N=73 n (%)	Titration N=70 n (%)	10 mg N=73 n (%)	Total N=216 n (%)
UDCA use	68 (93)	65 (93)	67 (92)	200 (93)
Daily UDCA dose, mg/kg	15 ± 4	17 ± 5	16 ± 5	16 ± 5
Age at diagnosis, years	47 ± 9	48 ± 12	47 ± 11	47 ± 11
<50 years	45 (62)	38 (54)	42 (58)	125 (58)
ALP, U/L	327 ± 115	326 ± 116	316 ± 104	323 ± 111
ALP >3x ULN	23 (32)	19 (27)	20 (27)	62 (29)
Bilirubin, µmol/L	12 ± 7	10 ± 6	11 ± 7	11 ± 7
Bilirubin >ULN	7 (10)	4 (6)	7 (10)	18 (8)
Moderately Advanced Disease Stage	13 (18)	12 (17)	11 (15)	36 (17)
Cirrhosis	9 (12)	7 (10)	4 (5)	20 (9)

Baseline data are Mean ± SD unless otherwise specified.

Cirrhosis defined as PBC Stage Four or fibrosis values of incomplete cirrhosis or cirrhosis on the baseline biopsy report.

Moderately advanced as defined per Rotterdam criteria

ALP ULN values based on criteria for females (118.3 U/L); Total Bilirubin ULN values based on criteria for females (19.32 µmol/L).

Comparison of Demographics and Baseline Characteristics

Double-Blind Phase 3 vs Global PBC Study Group

	PBC Patients (Untreated or UDCA-treated)	
	Double-Blind Phase 3 N=216	Global PBC Study Group ^a N=4845
Age at entry (years)^b	55.8 (10.48)	54.5 (12.0)
Duration of PBC^c	8.3 (3.1 - 12.1)	7.3 (3.6 - 11.5)
Female, n (%)	196 (91)	4348 (90)
UDCA-treated patients, n (%)	200 (93)	4119 (85)
Baseline ALP		
Serum ALP (xULN)^c	2.42 (2.01, 3.15)	2.10 (1.31 ,3.72)
>3x ULN, n (%)	62 (29)	606 (16)
Baseline Serum Bilirubin		
Serum Bilirubin (xULN)^c	0.56 (0.36, 0.66)	0.67 (0.45-1.06)
>ULN, n (%)	18 (8)	740 (20)
Biochemical disease stage, n (%)		
Early: bilirubin ≤ULN and albumin ≥LLN	174 (80)	2040 (67)
Moderately Advanced: abnormal bilirubin or albumin	36 (17)	730 (24)
Advanced: abnormal bilirubin and albumin	6 (3)	259 (9)

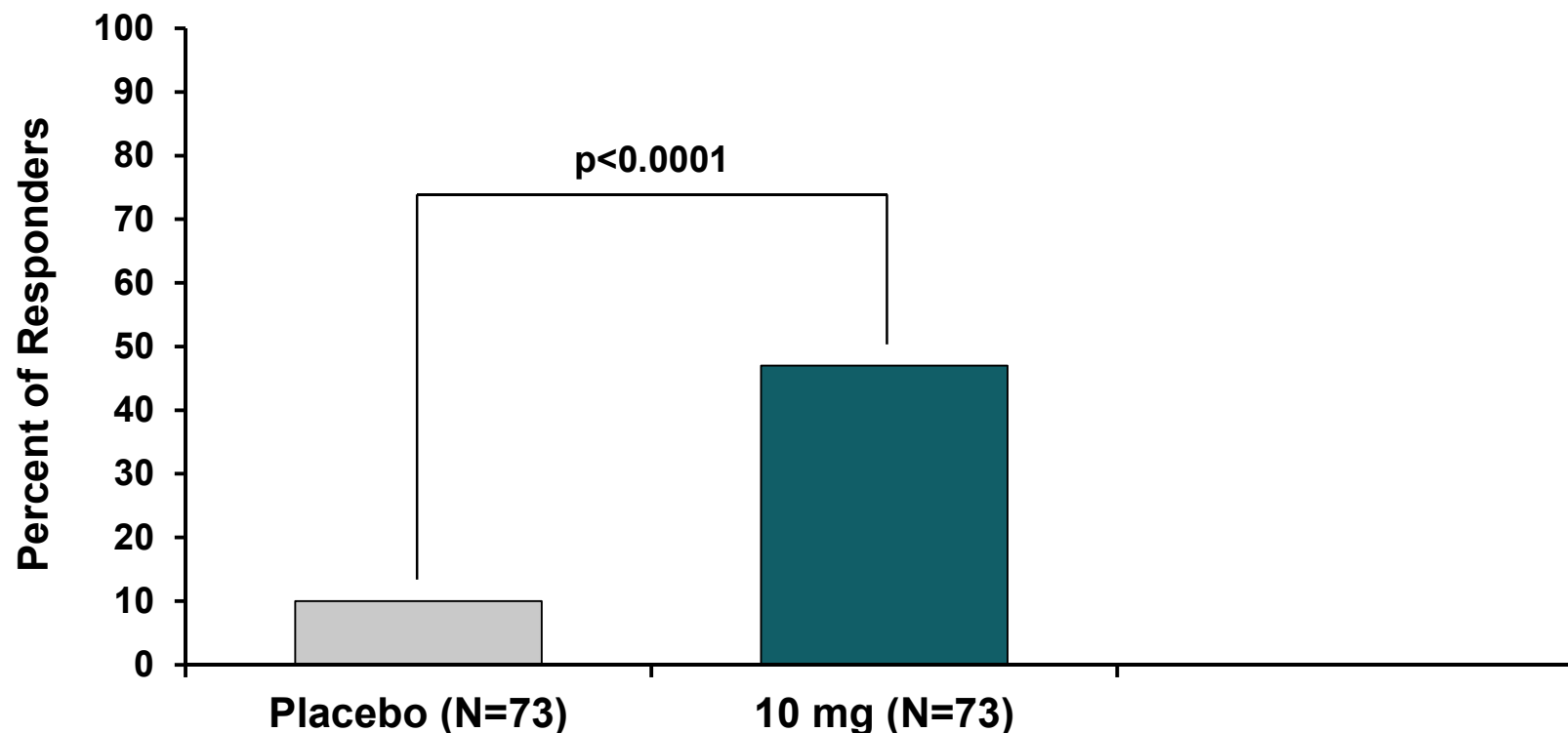
^a Lammers WJ et al. *Gastroenterology*. 2014 Dec;147 (6):1338-1349.e5. doi: 10.1053/j.gastro.2014.08.029.

^b Mean (SD)

^c Median (Q1, Q3)

Primary Endpoint Achieved

Double-Blind Phase 3 – Month 12



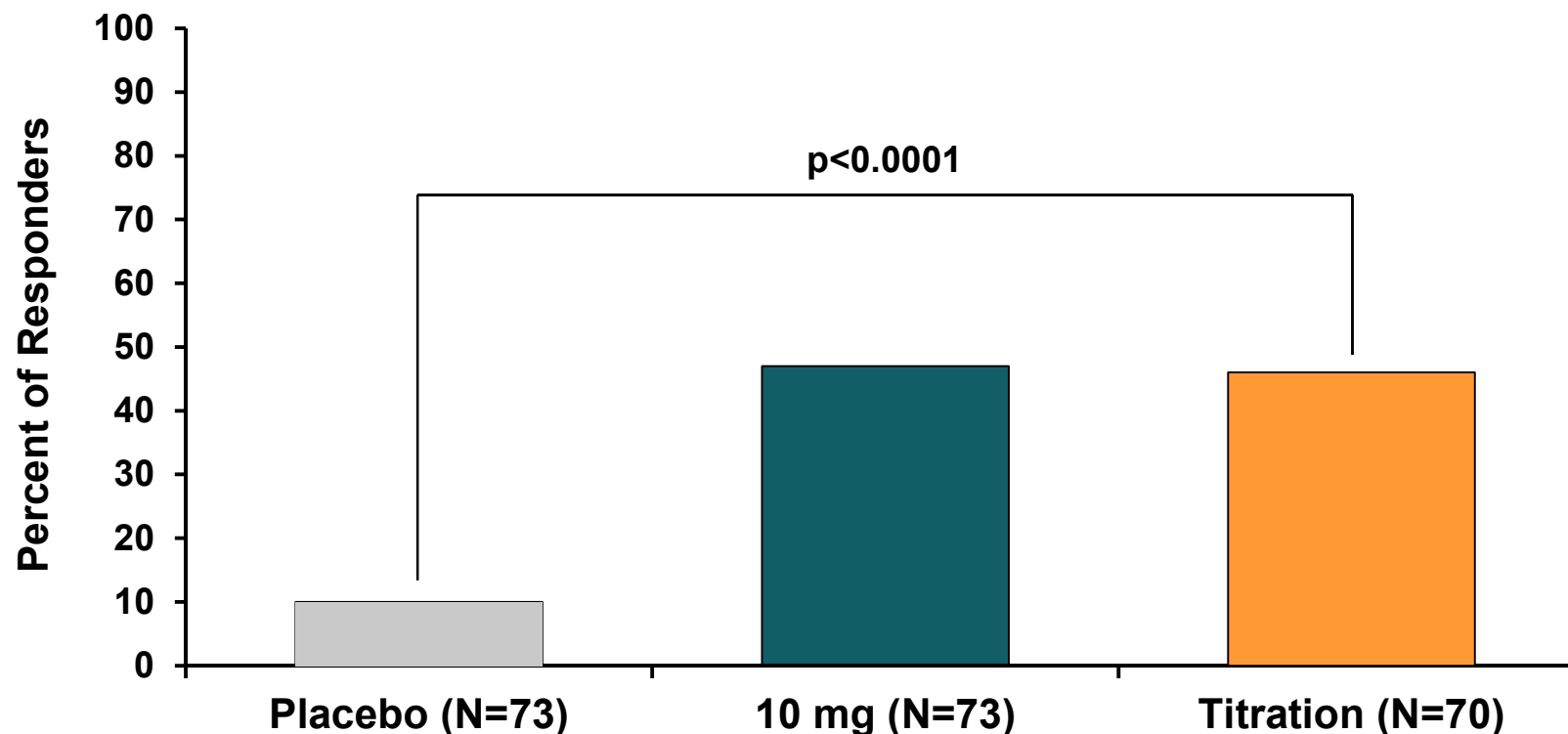
Primary Endpoint:

Proportion of patients achieving ALP $< 1.67 \times \text{ULN}$ with bilirubin $\leq \text{ULN}$ and $\geq 15\%$ reduction in ALP

Missing values were considered a non-response. P-value obtained using CMH test stratified by randomization strata factor.

Primary Endpoint Achieved

Double-Blind Phase 3 – Month 12



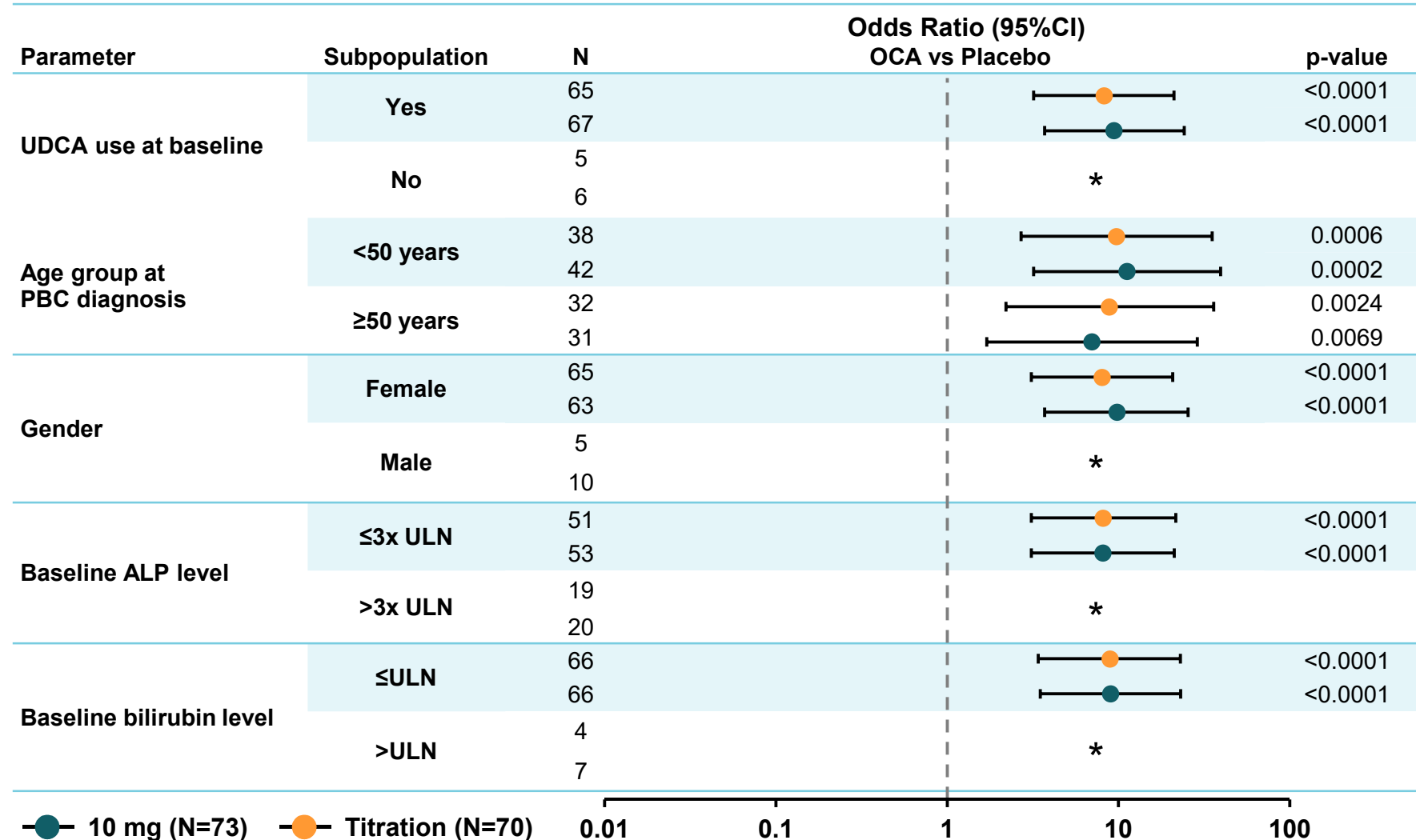
Primary Endpoint:

Proportion of patients achieving ALP <1.67x ULN with bilirubin ≤ULN and ≥15% reduction in ALP

Missing values were considered a non-response. P-value obtained using CMH test stratified by randomization strata factor.

Response by Subpopulation

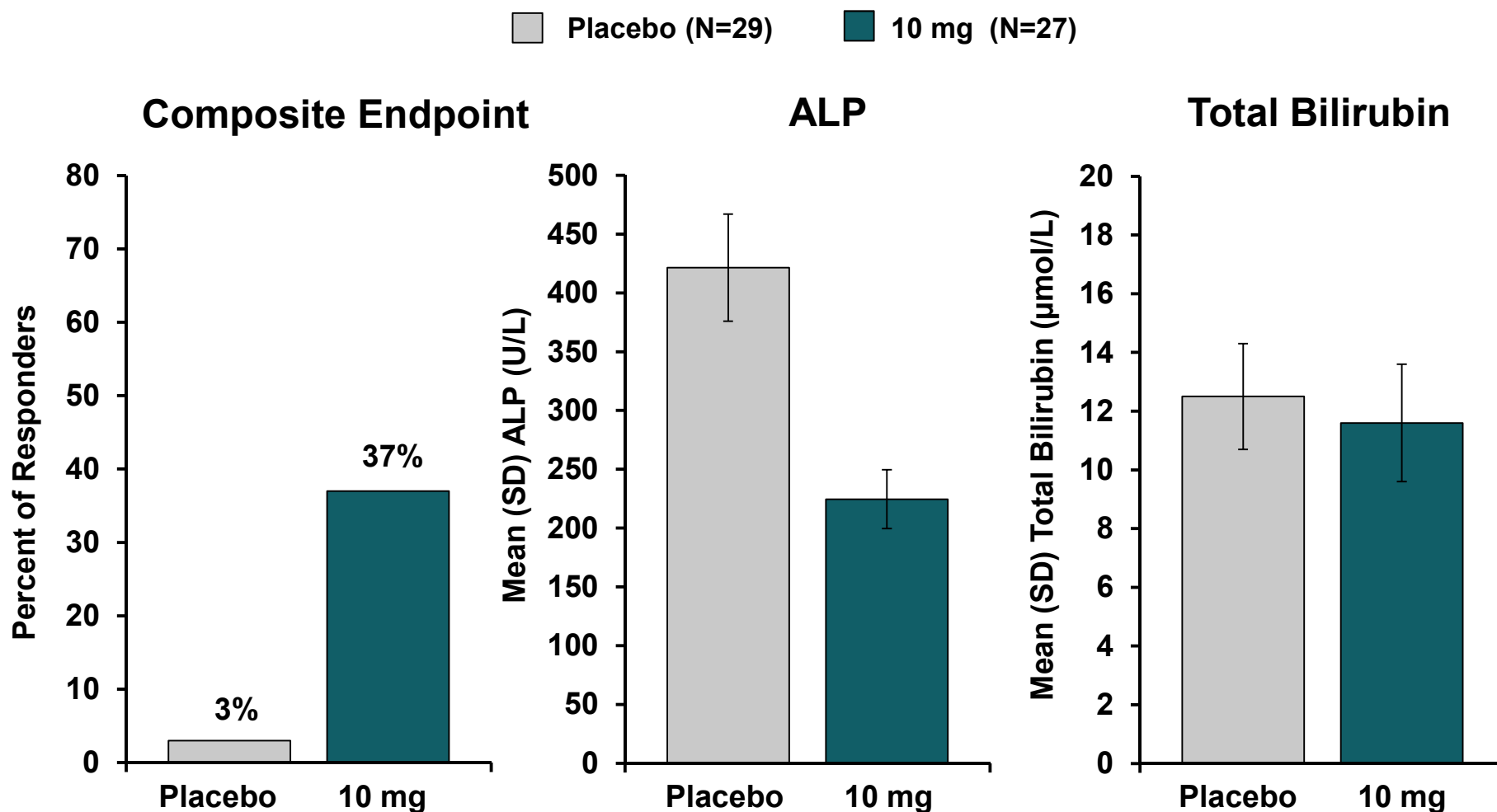
Double-Blind Phase 3 – Month 12



*No placebo responders

Efficacy of OCA as Monotherapy

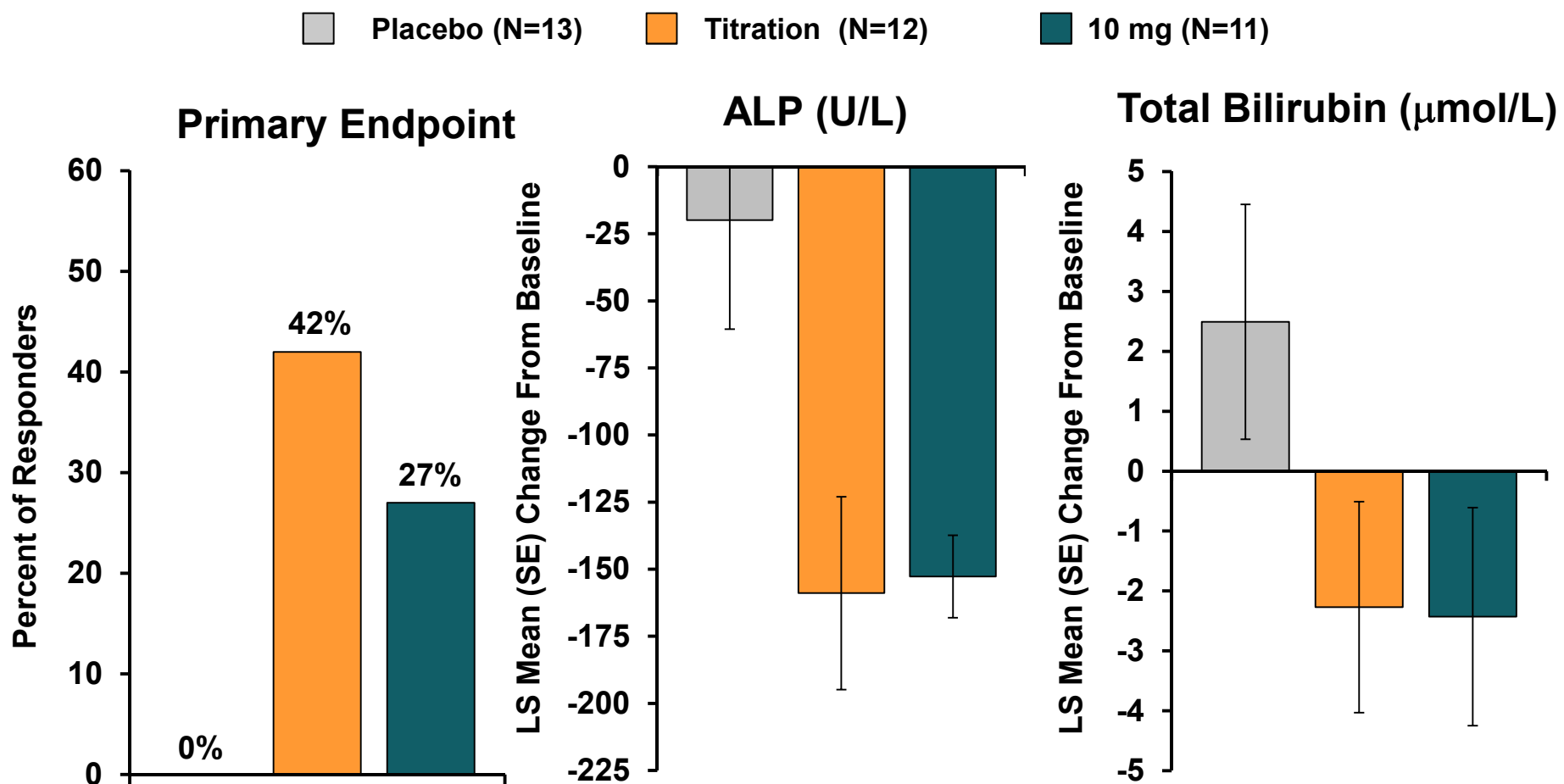
Double-Blind Studies (Pooled) – Month 3



Difference from placebo statistically significant for all 3 parameters.

Efficacy in Moderately Advanced Patients

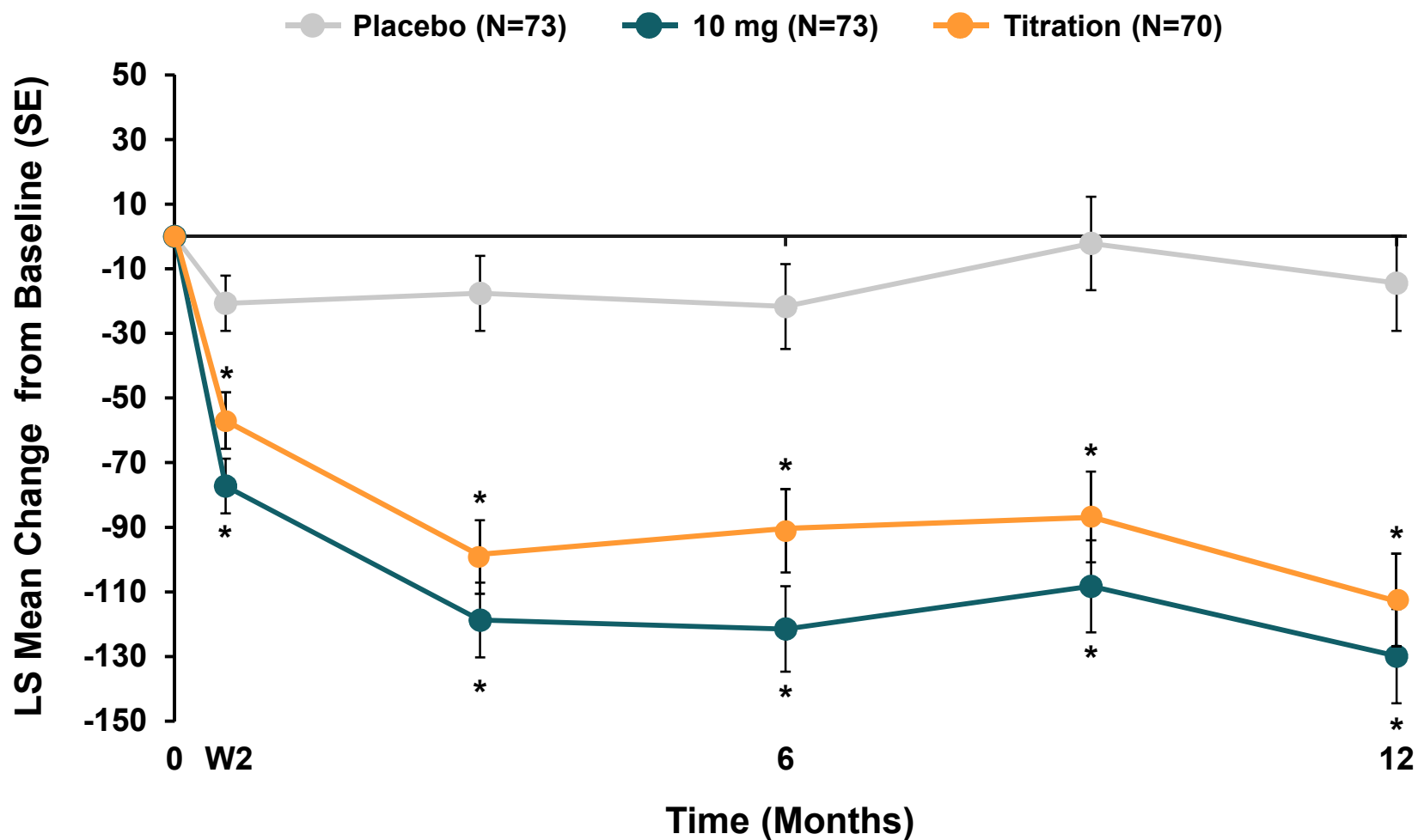
Double-Blind Phase 3 – Month 12



Rotterdam Criteria (moderate): total bilirubin or albumin is abnormal.

Reductions in ALP (U/L) Were Observed Early and Sustained

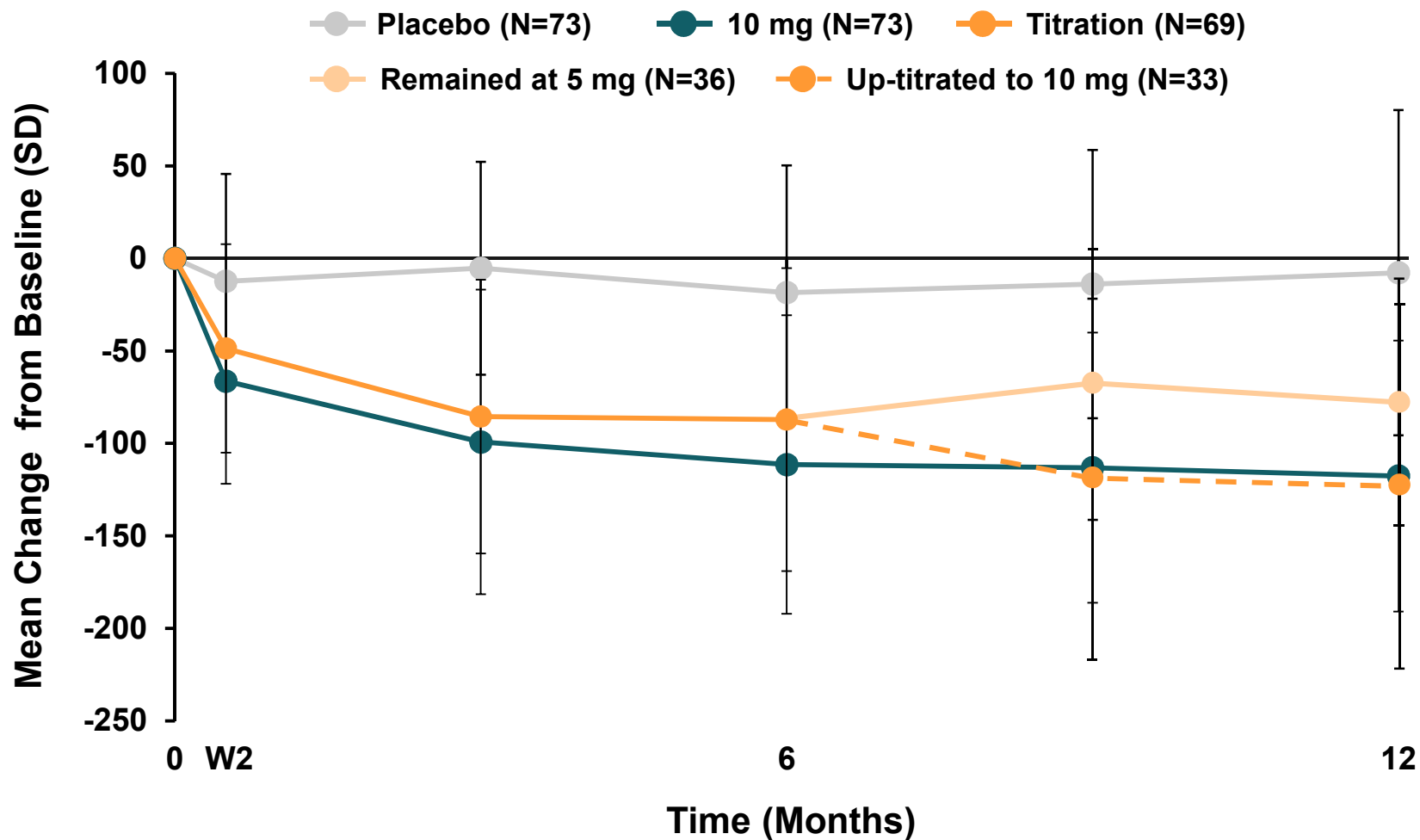
Double-Blind Phase 3



*p<0.0001

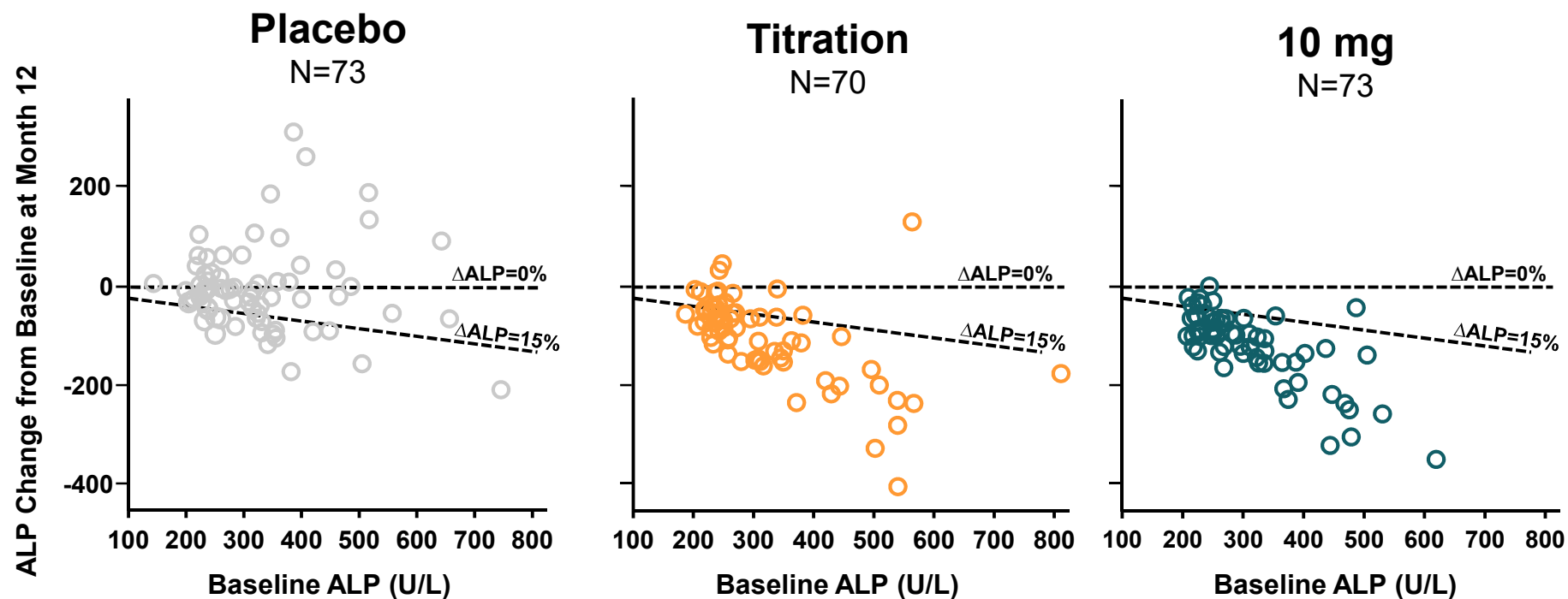
OCA Titration Following Month 6 Resulted in Incremental Improvement in ALP

Double-Blind Phase 3



Majority of OCA-Treated Patients Had Improvement in ALP

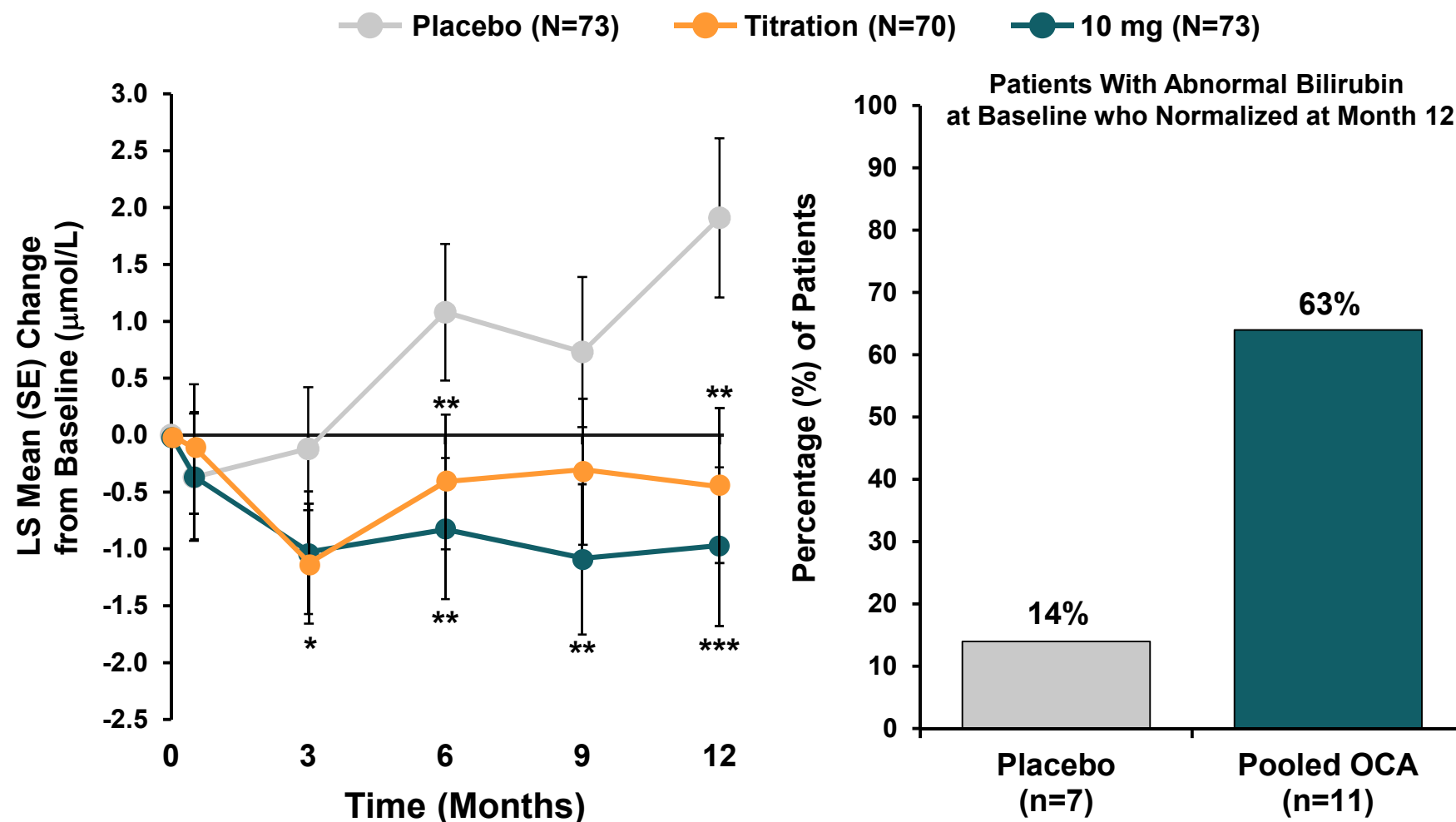
Double-Blind Phase 3 – Baseline vs Month 12



- 29% of placebo patients saw at least a 15% ALP improvement - compared with 77% of OCA patients
- 36% of placebo patients experienced an increase in ALP - compared with only 3% of OCA patients

Total Bilirubin Maintained Over Time in OCA-Treated Patients

Double-Blind Phase 3



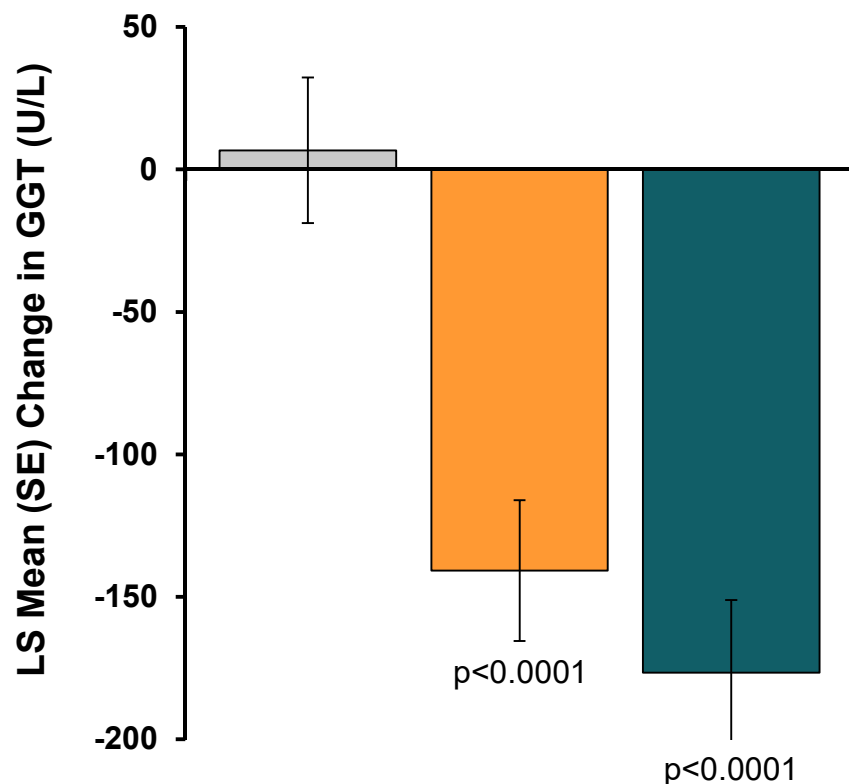
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$

OCA Treatment Improves Additional Marker of Cholestasis – GGT

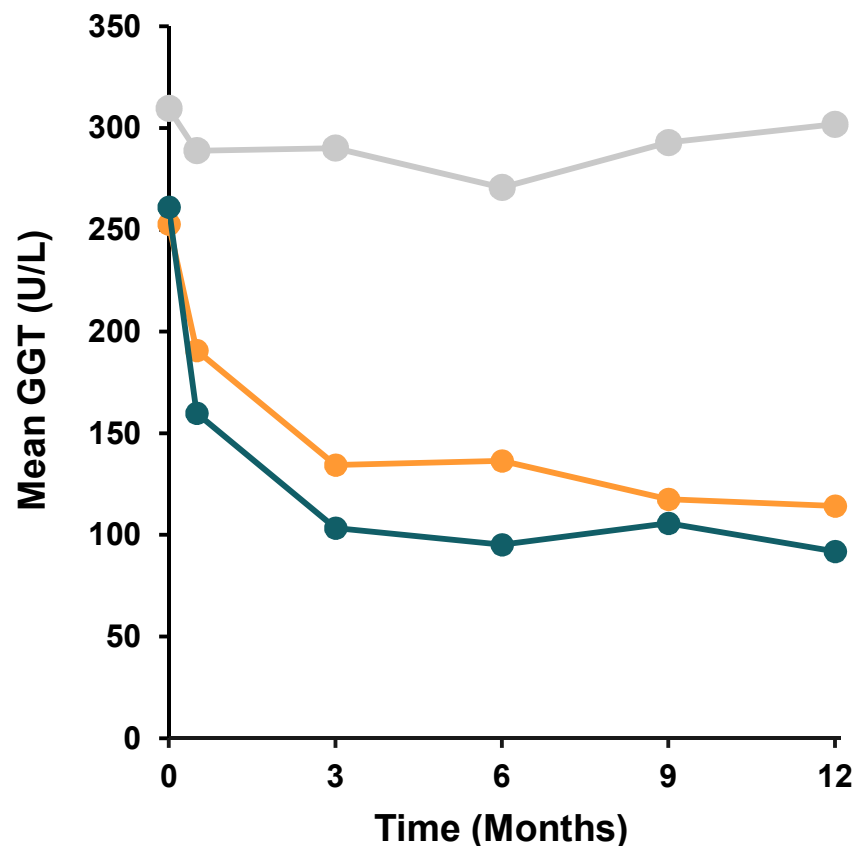
Double-Blind Phase 3

Placebo (N=73) Titration (N=70) 10 mg (N=73)

**LS Mean Change in GGT (U/L)
From Baseline to Month 12**

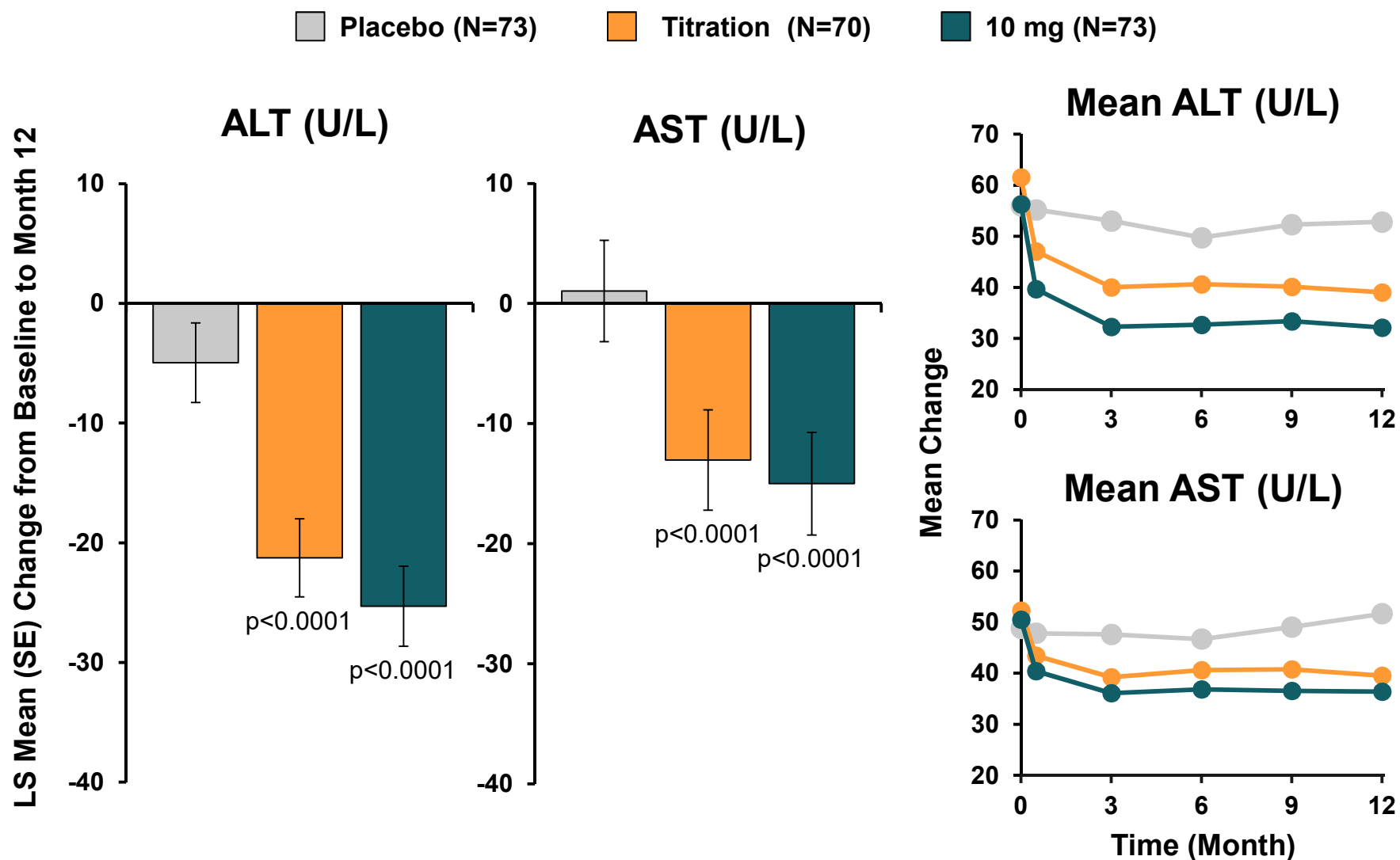


Mean GGT (U/L)



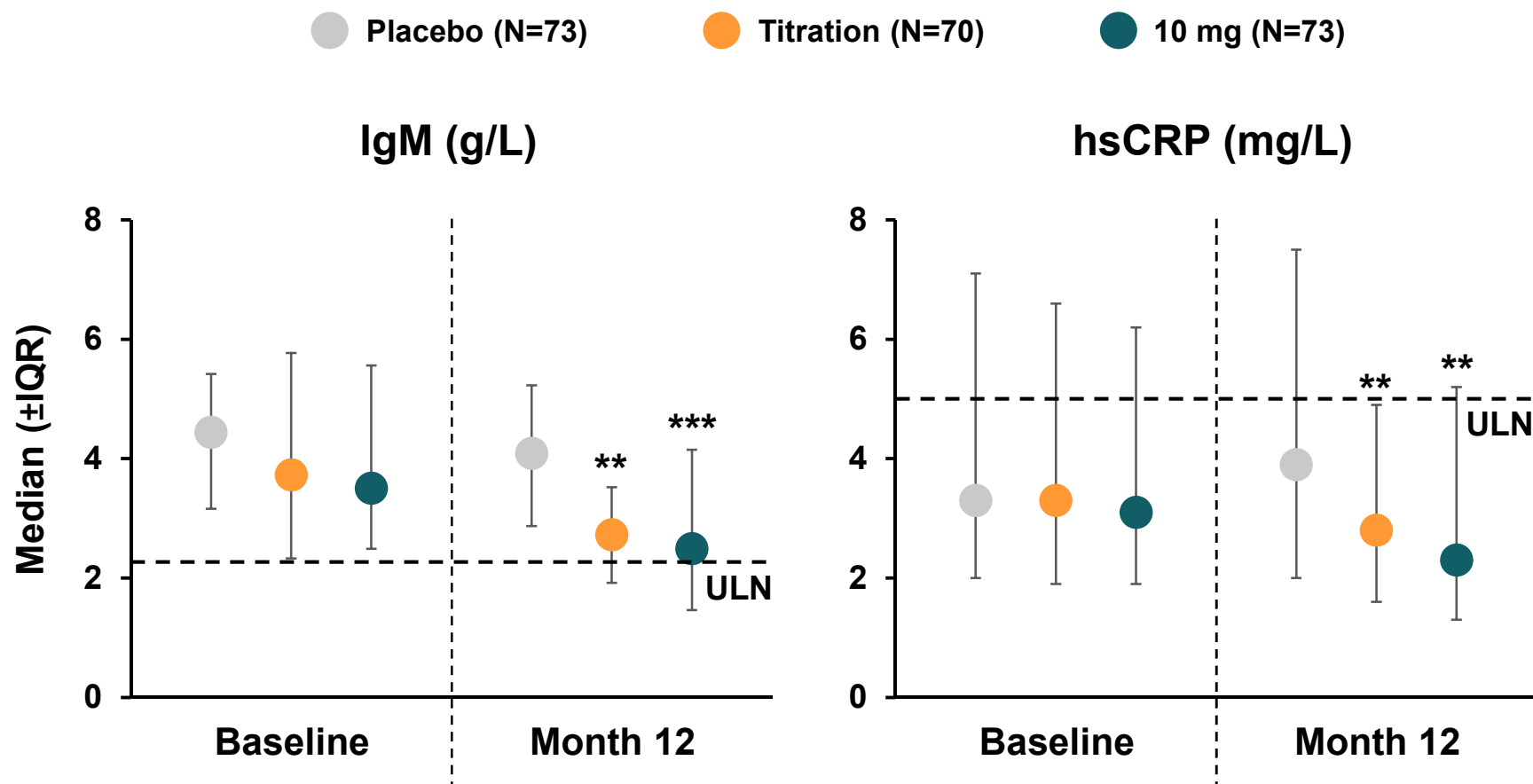
OCA Treatment Improves Markers of Hepatobiliary Damage

Double-Blind Phase 3



Improvement in Immunological and Inflammation Markers

Double-Blind Phase 3



Hodges-Lehmann estimates for the median difference (OCA - Placebo).

p<0.01, *p<0.0001; p-value for comparing OCA treatments to placebo was obtained using the Wilcoxon rank-sum test.

Clinical Outcomes

Double-Blind Phase 3

Randomized Treatment
n (%)

Double-Blind Phase

Placebo
3 (4)

Upper GI Bleeding
2 events of Esophageal Varices

MELD ≥ 15

MELD ≥ 15

Pooled OCA
3 (2)

Upper GI Bleeding

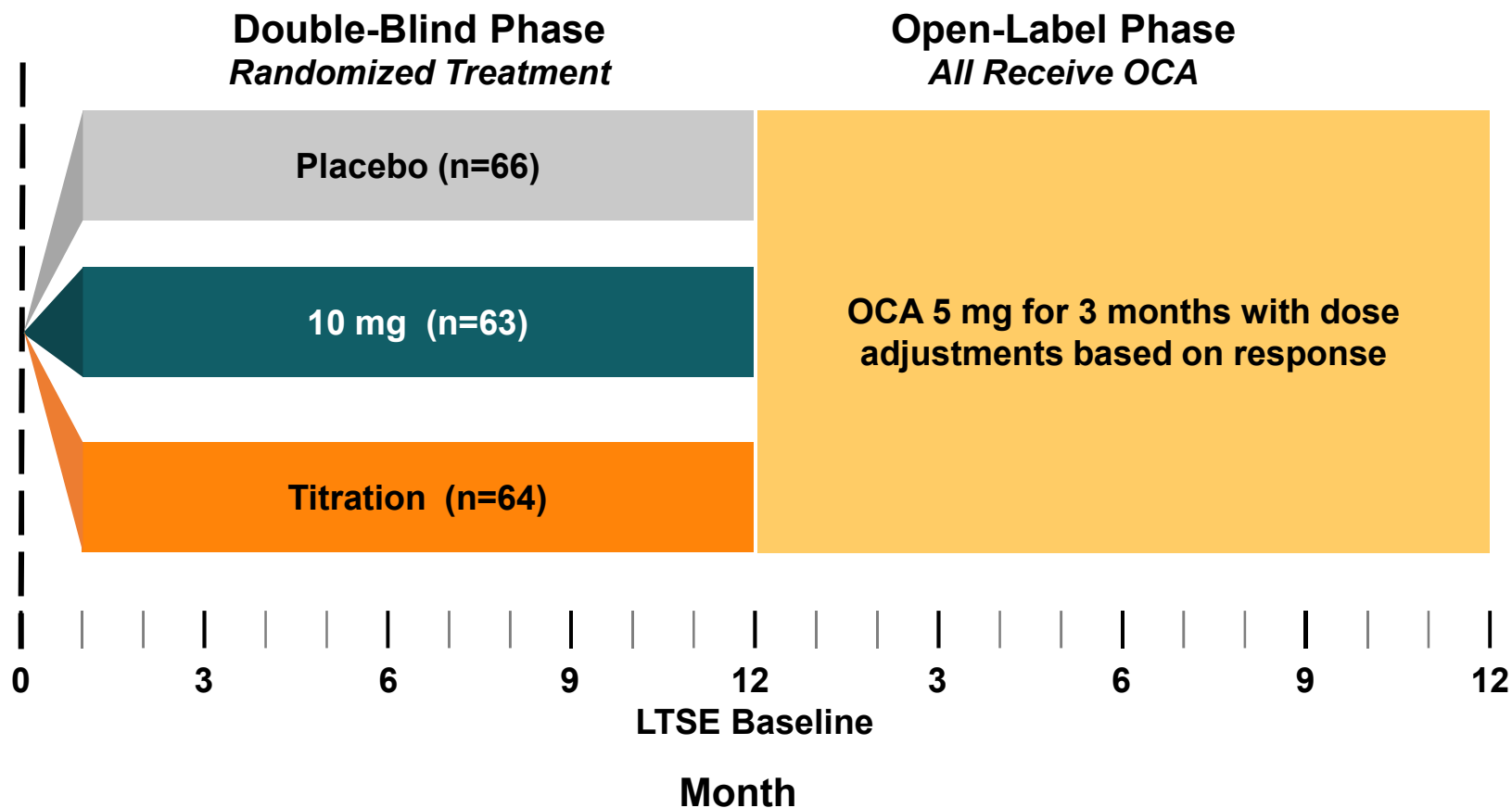
Hepatic Encephalopathy
Ascites

Death

Study Design

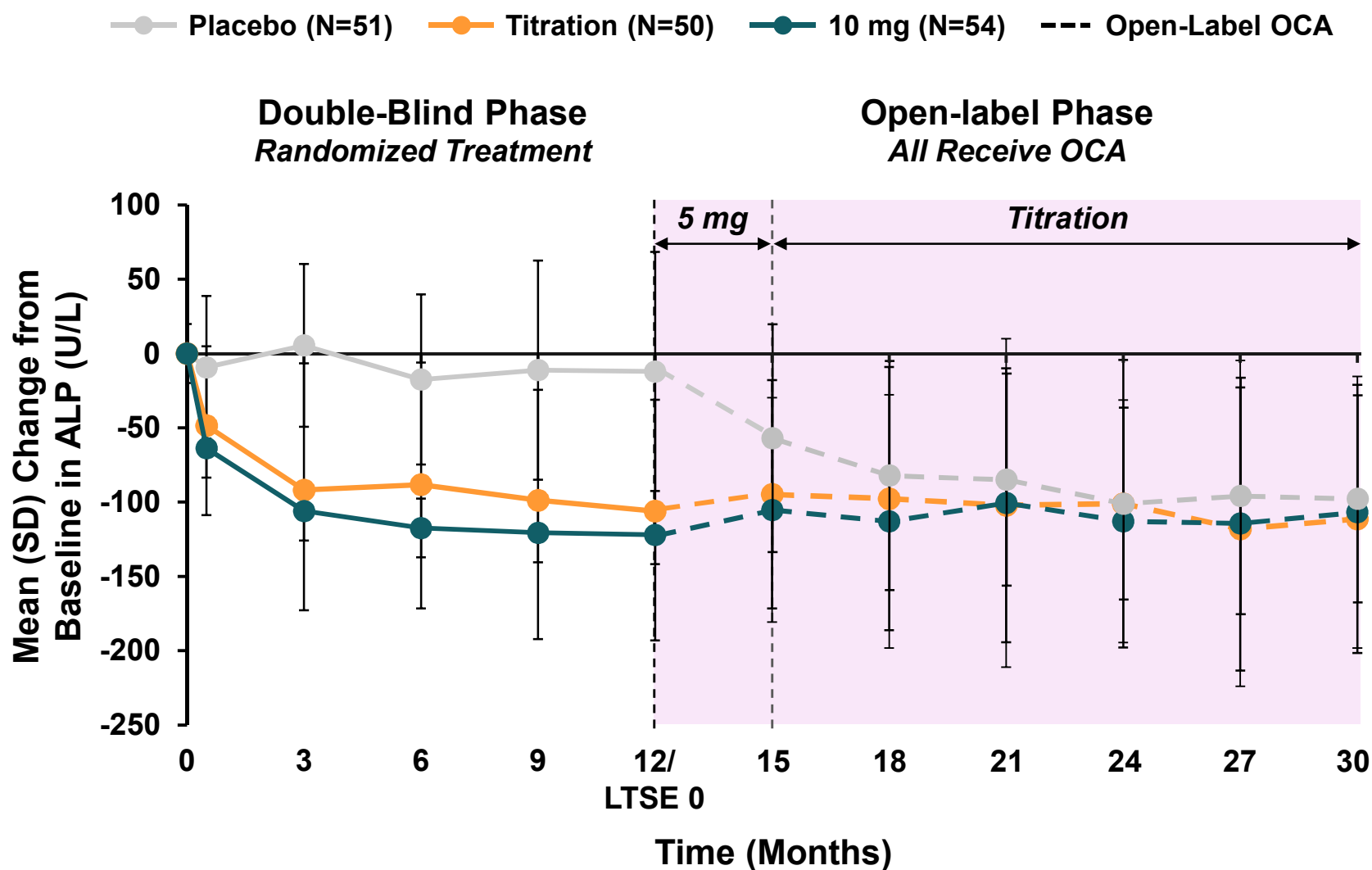
Long-Term Safety Extension (LTSE) Phase 3

Enrolled into Long-Term Safety Extension (N = 193)



OCA Treatment Durable – ALP

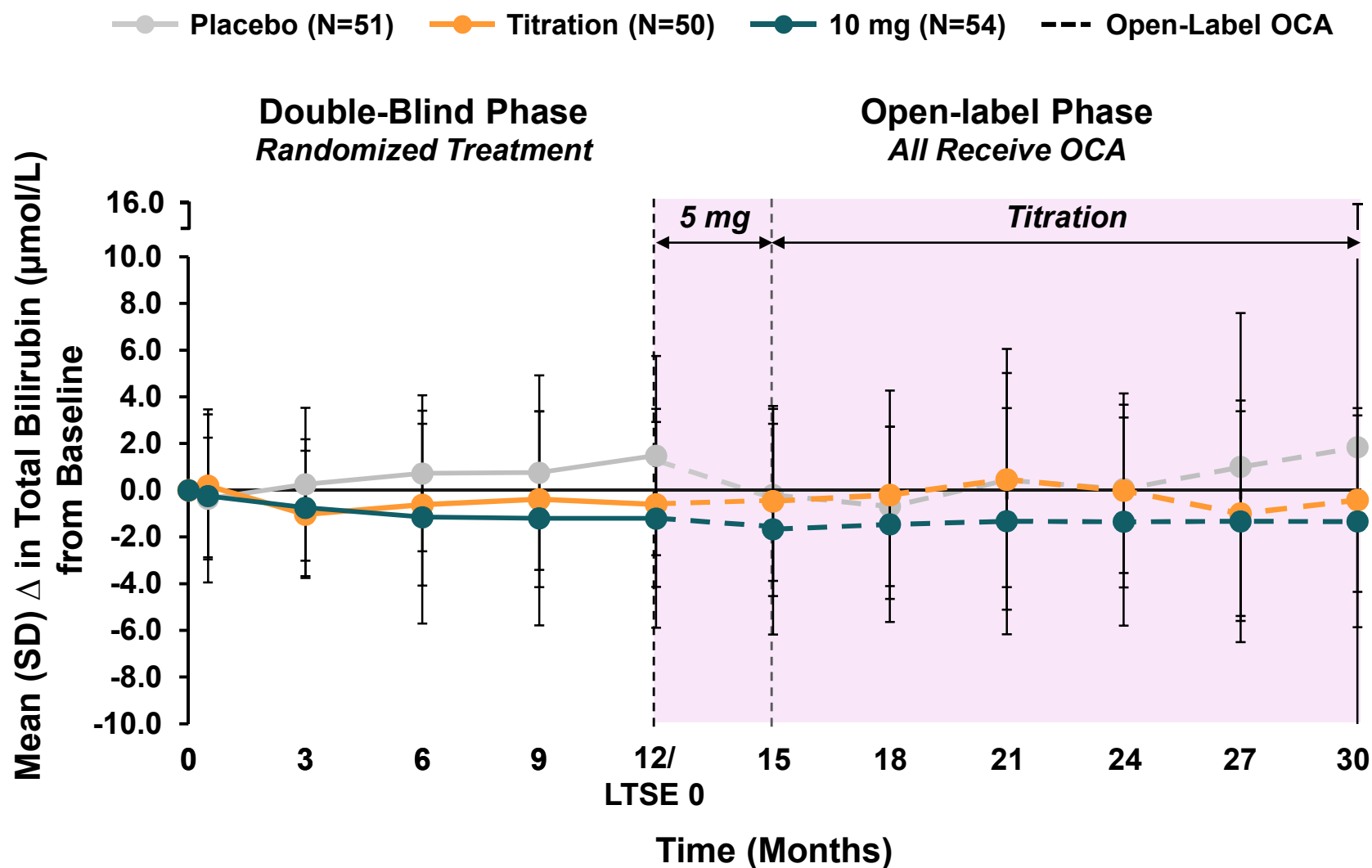
Long-Term Safety Extension (LTSE) Phase 3



Data are summarized by randomized treatment and by weighted average daily OCA dose ≤10 mg.

OCA Treatment Durable – Total Bilirubin

Long Term Safety Extension (LTSE) Phase 3



Data are summarized by randomized treatment and by weighted average daily OCA dose ≤ 10 mg.

OCA Represents Promising Novel Treatment for PBC

- Significant increase in proportion of patients achieving primary endpoint
- Clinically meaningful improvements in markers of
 - Cholestasis, hepatic function, hepatobiliary damage, and inflammation
- Consistent results across high risk subpopulations
- Durable efficacy with longer-term treatment
- Starting subjects at 5-mg OCA and titration to 10-mg OCA is an appropriate dosing strategy

Safety of OCA in Patients with PBC

Roya Hooshmand-Rad, MD, PhD

Intercept Pharmaceuticals, Inc.

Executive Director

Medical Safety and Pharmacovigilance

OCA Exposure

Intercept Sponsored and Investigator Initiated Studies

	N	Mean Years	Patient Exposure Years
All PBC Studies	432	1.6	675

**Clinical
pharmacology
studies**

N=844

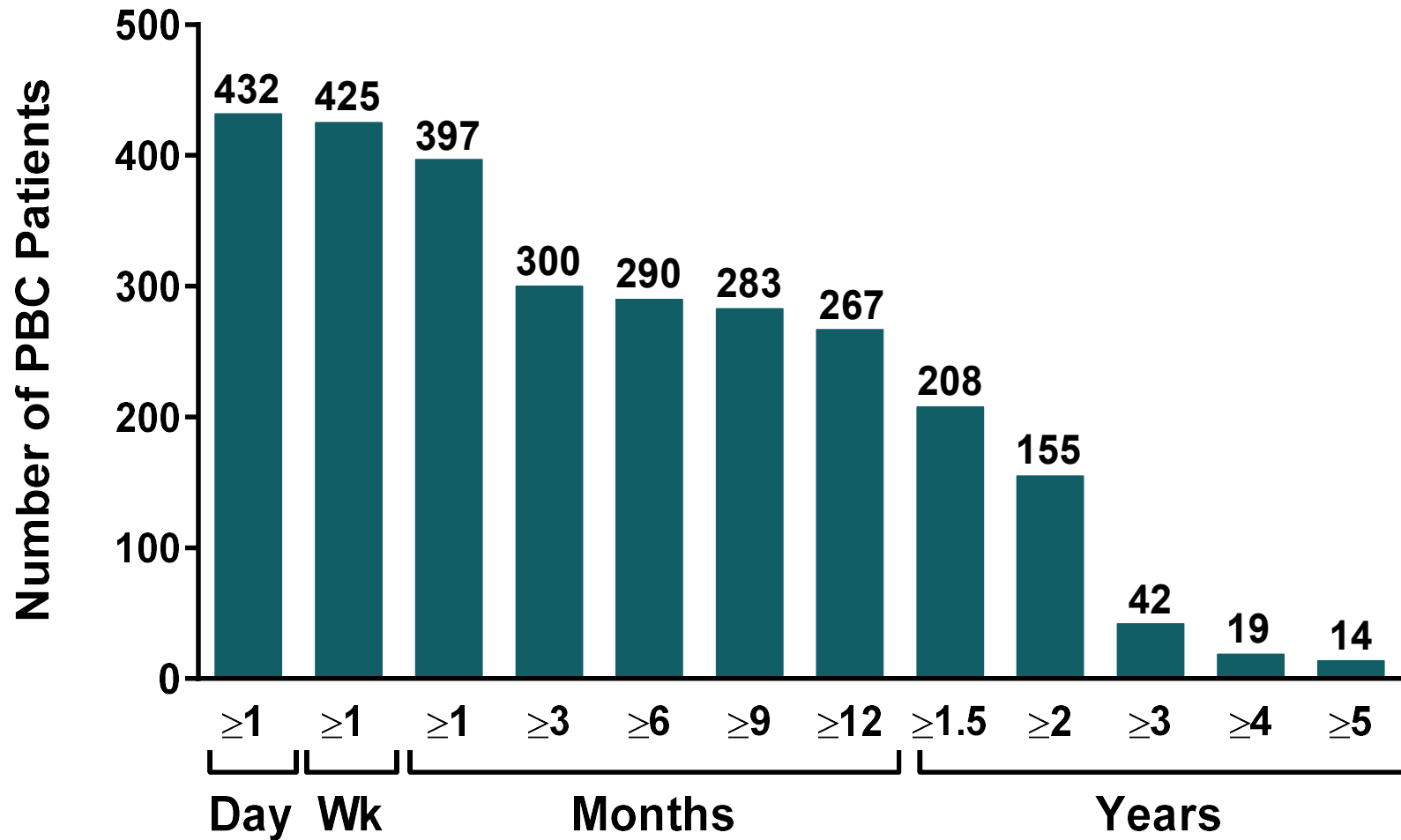
**Intercept sponsored
for other indications**

N=74

**Investigator
initiated studies**

N=305

OCA Exposure in Patients with PBC



Patient Disposition

Double-Blind Phase 3

	Placebo N=73 n (%)	Titration N=71 n (%)	10 mg N=73 n (%)
All treated population	73 (100)	70 (99)	73 (100)
Completed DB phase	70 (96)	64 (90)	64 (88)
Completed DB and entered LTSE	66 (94)	63 (98)	64 (100)
Overall discontinuations due to AE	3 (4)	5 (7)	8 (11)
Due to pruritus	0	1 (1)	7 (10)

Overall Summary of Adverse Events

Double-Blind Phase 3

	Placebo N=73 n (%)	Titration N=70 n (%)	10 mg N=73 n (%)
Patients with AE	66 (90)	65 (93)	69 (95)
Patients with SAE	3 (4)	11 (16)	8 (11)
Death	0	1 (1)	0

Serious Adverse Events

Double-Blind Phase 3

Preferred Term	Placebo N=73 n (%)	Titration N=71 n (%)	10 mg N=73 n (%)
All SAEs	3 (4)	11 (16)	8 (11)
SAEs >1 patient			
Varicose vein	0	2 (3)	0
Osteoarthritis	0	0	2 (3)

~80% OCA-treated patients with SAE continued long term treatment

Adverse Drug Reactions

Double-Blind Phase 3

ADRs Category	Placebo N=73 n (%)	Titration N=70 n (%)	10 mg N=73 n (%)
Pruritus/skin eruptions	28 (38)	39 (56)	51 (70)

Adverse Drug Reactions

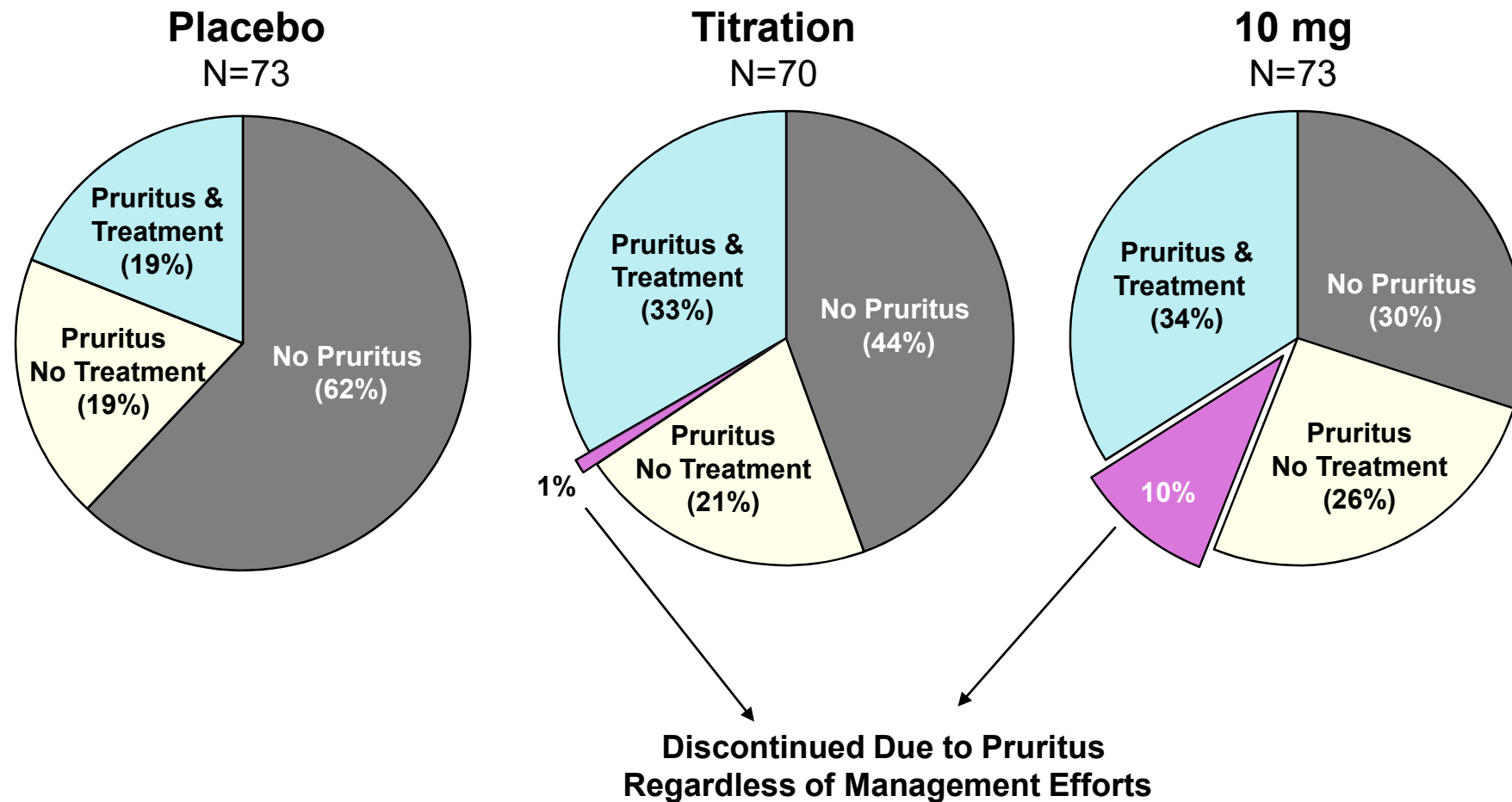
Double-Blind Phase 3

ADRs Category	Placebo N=73 n (%)	Titration N=70 n (%)	10 mg N=73 n (%)
Pruritus	28 (38)	39 (56)	51 (70)
Fatigue/tiredness	11 (15)	13 (19)	18 (25)
Abdominal pain and discomfort	10 (14)	13 (19)	7 (10)
Rash and urticaria	6 (8)	5 (7)	7 (10)
Oropharyngeal pain	1 (1)	5 (7)	6 (8)
Dizziness	4 (5)	5 (7)	5 (7)
Constipation	4 (5)	5 (7)	5 (7)
Arthralgia	3 (4)	4 (6)	7 (10)
Cough	5 (7)	4 (6)	6 (8)
Thyroid function abnormality	2 (3)	4 (6)	3 (4)
Eczema	0	4 (6)	2 (3)
Procedural pain	1 (1)	4 (6)	1 (1)
Edema peripheral	2 (3)	2 (3)	5 (7)
Palpitations	1 (1)	2 (3)	5 (7)
Pyrexia	1 (1)	0	5 (7)

ADRs=events that occurred in $\geq 5\%$ in either OCA treatment group and occurring in $\geq 1\%$ more than in placebo

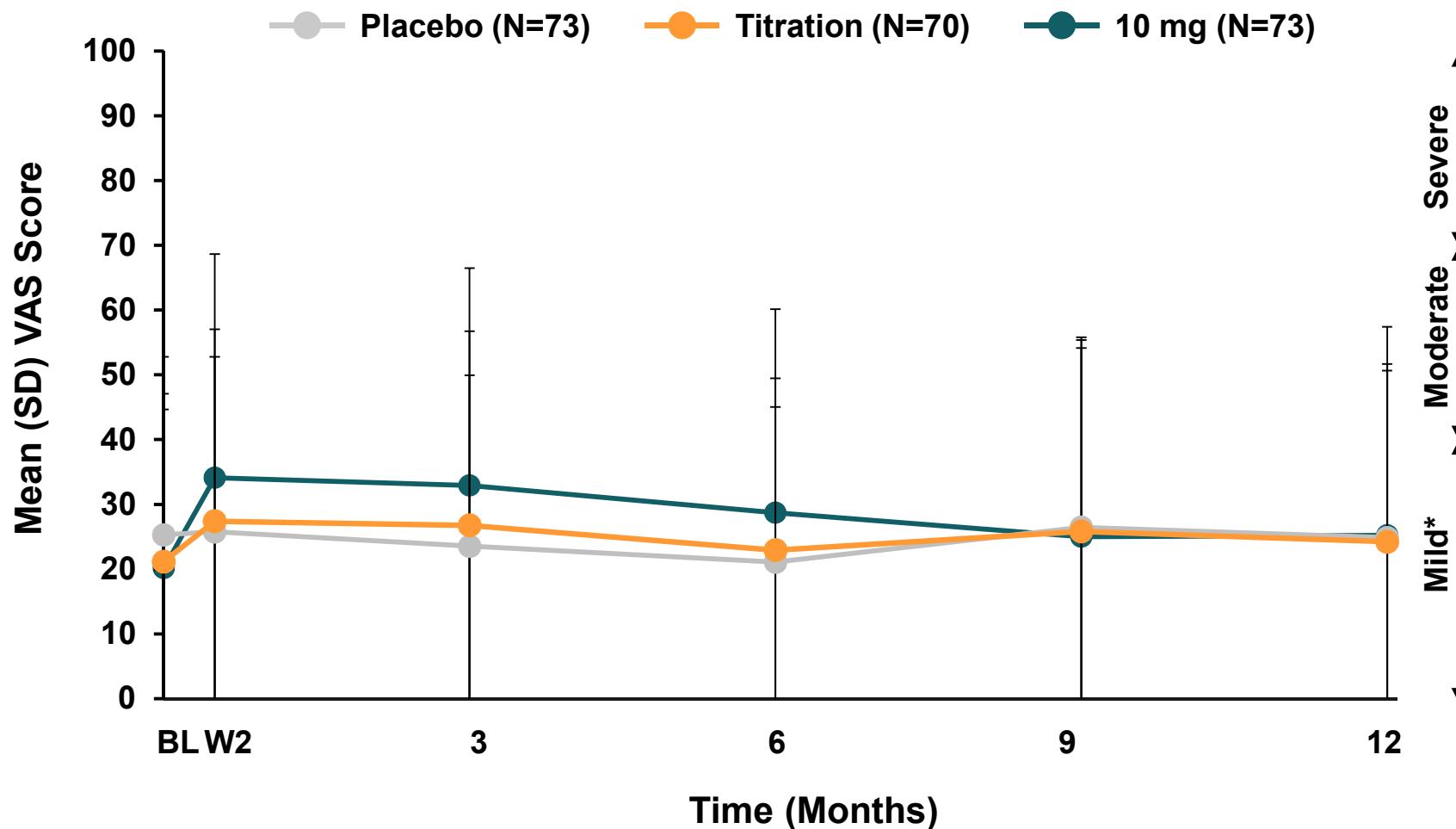
Pruritus as an Adverse Event

Double-Blind Phase 3



Patient Experience: Visual Analog Scale

Double-Blind Phase 3



Last observation is carried forward

*Reich et al Acta Derm 2012

Hepatic Adverse Events

Double-Blind Phase 3

	Placebo N=73 n (%)	Titration N=70 n (%)	10 mg N=73 n (%)
All patients with hepatic AEs*	2 (3)	3 (4)	2 (3)
Patients with clinical hepatic AEs	1 (1)	2 (3)	1 (1)
Ascites	0	1 (1)	1 (1)
Hepatic encephalopathy	0	1 (1)	0
Varices esophageal	1 (1)	1 (1)	0
Patient with other hepatic AEs	0	0	2 (3)
Hepatic pain	0	0	1 (1)
Spider nevus	0	0	1 (1)
Patients with biochemical hepatic AEs‡	1 (1)	1 (1)	0
International normalized ratio increased	0	1 (1)	0
Liver function test abnormal	1 (1)	0	0

*Standardized MedDRA query of Hepatic Disorders

‡Events reported as AEs by the investigator (not laboratory values)

CTCAE Graded Serum Liver Abnormalities

Double-Blind Phase 3

	Placebo N=73 n (%)	Titration N=70 n (%)	10 mg N=73 n (%)
ALT			
CTCAE grade 3	6 (8)	1 (1)*	0
CTCAE grade 4	0	0	0
AST			
CTCAE grade 3	2 (3)	1 (1)*	0
CTCAE grade 4	0	0	0

*Total bilirubin remained within normal limits

No Grade 3 or 4 Bilirubin increase in any arm (no elevation >3X ULN)

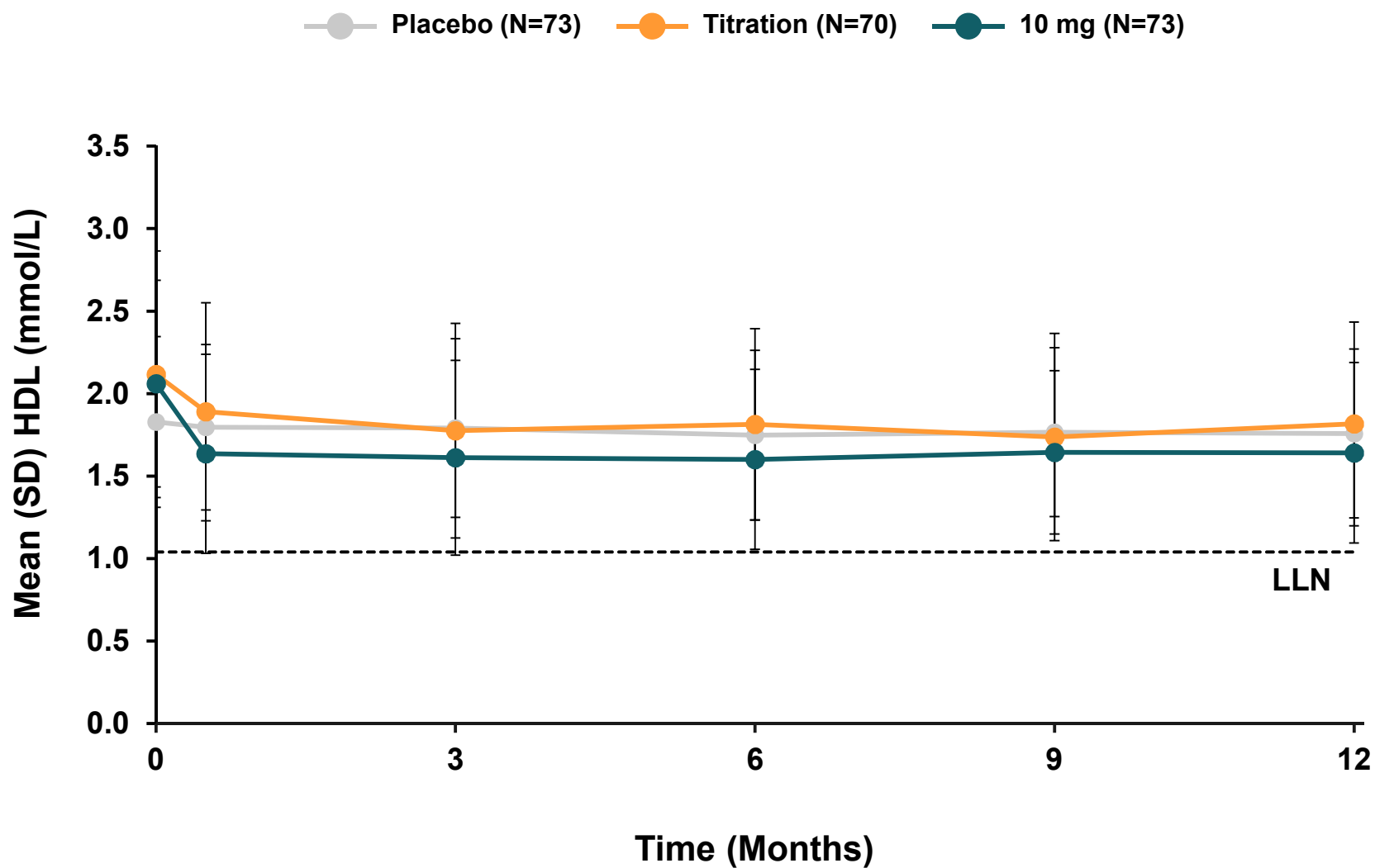
CTCAE=Common Terminology Criteria for Adverse Events

CTCAE grades (version 4.03): 1 ≥ULN - 3.0 x ULN, 2 ≥3.0 - 5.0 x ULN, 3 ≥5.0 - 20.0 x ULN, 4 ≥20.0 x ULN.

For females: AST ULN = 25.7 U/L, ALT ULN = 22.9 U/L. For males: AST ULN = 33 U/L, ALT ULN = 33.4 U/L.

HDL Over Time

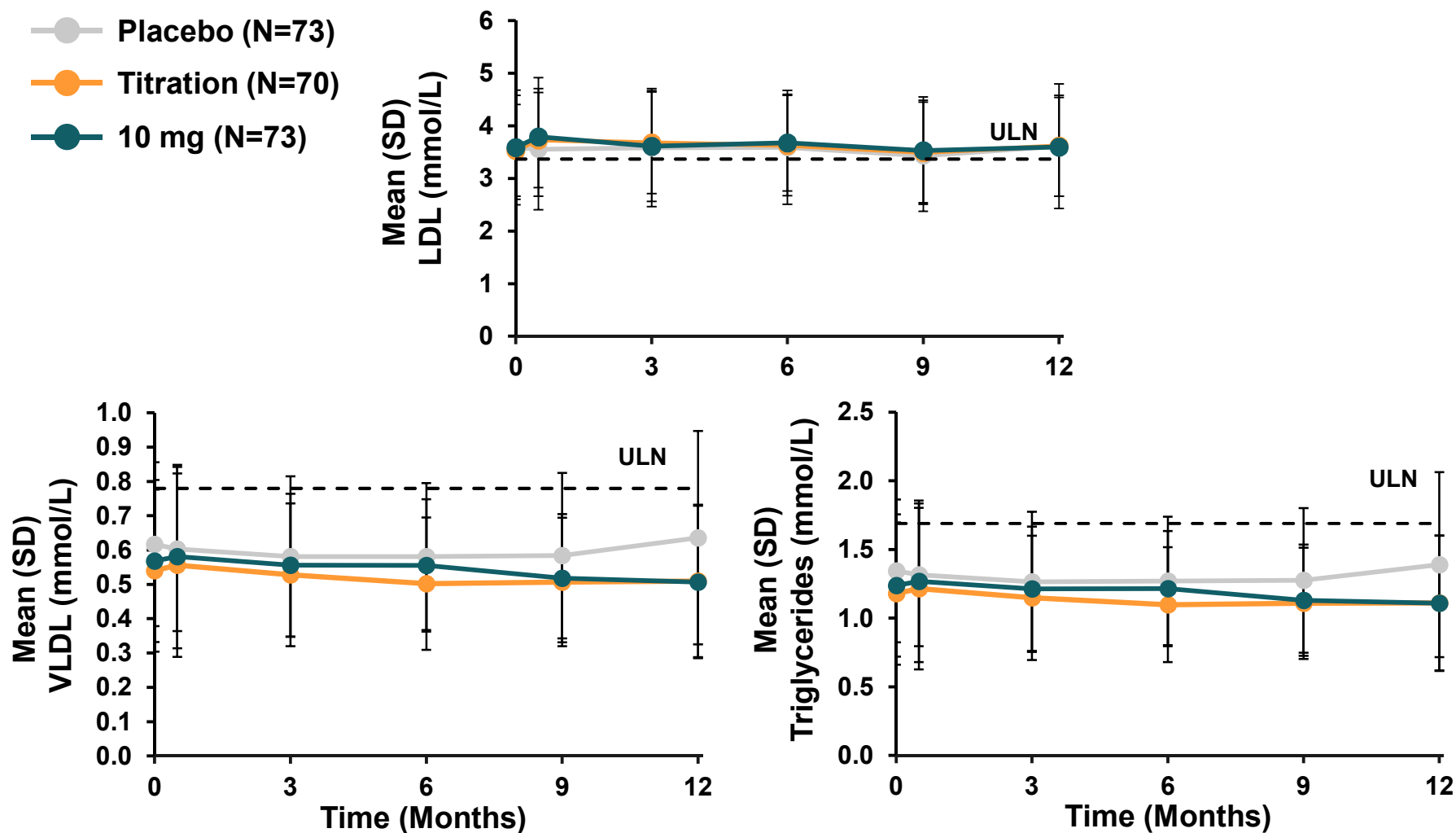
Double-Blind Phase 3



LLN=Lower Limit of Normal

TG, VLDL and LDL Over Time

Double-Blind Phase 3



TG: Triglycerides; VLDL: very low density lipoprotein; LDL: low density lipoprotein

Long Term Safety

LTSE Phase 3

- No new category of safety observations with long term use
- Pruritus: most common AE
 - Single most common reason for discontinuation (3%)
- No pattern in SAEs occurring with long term exposure
- SAEs occurring in 2 or more patients were
 - Osteoarthritis (3%)
 - Variceal bleeding (2%)
- One fatal event
- Lipid levels remained stable

OCA Generally Well Tolerated in Patients With PBC

- Pruritus most frequent AE
 - Tolerable with 1 discontinuation in titration arm
- Infrequent hepatic events
- Early changes in HDL
 - Stabilize within months with continued treatment
 - Overall remain within normal limits
- Small transient increase in LDL
 - Comparable to placebo by end of study
- AE profile stable with long-term treatment
 - No new signals with longer treatment

Benefit-Risk

John M. Vierling, MD FACP, FAASLD

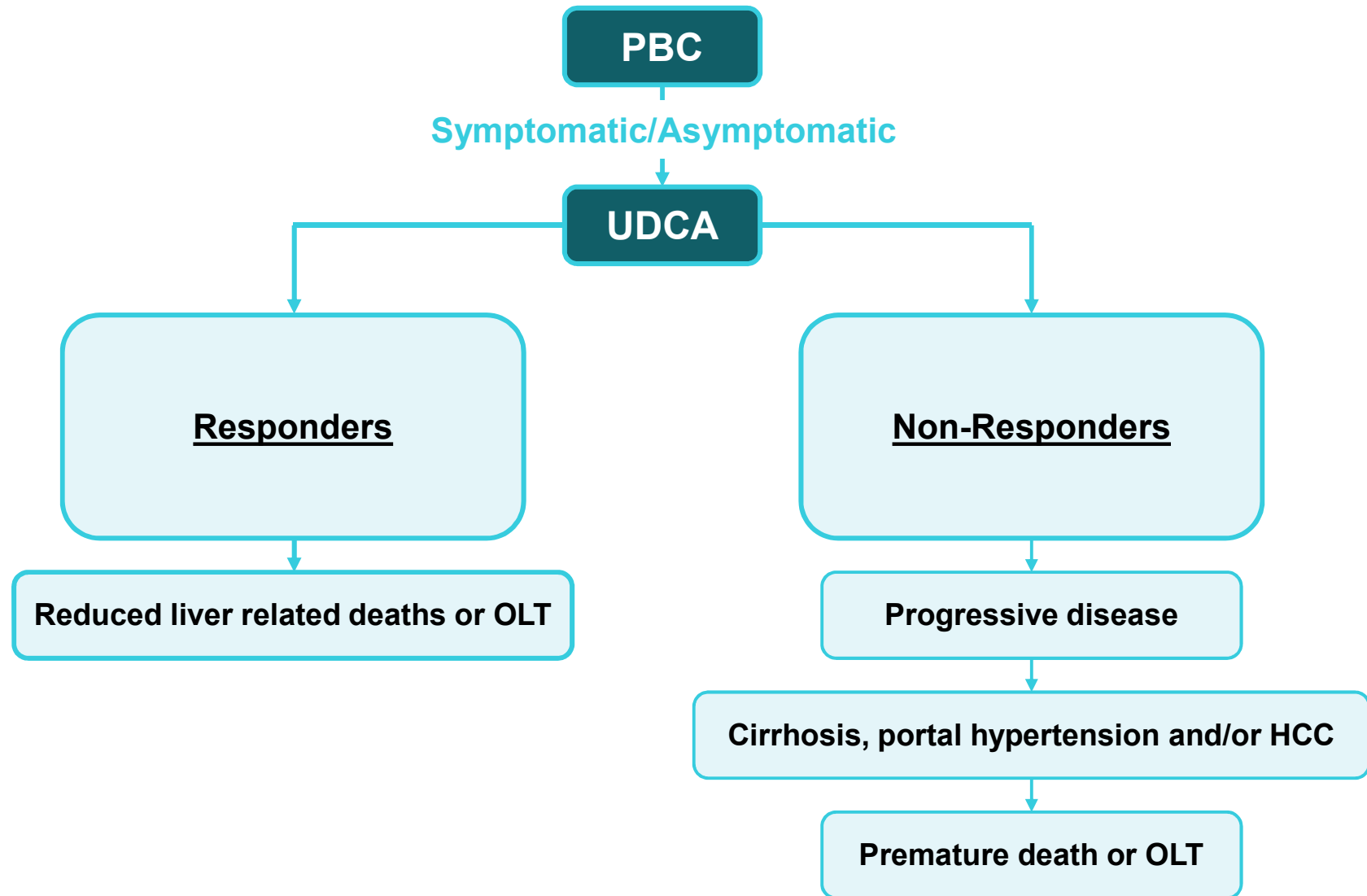
Baylor College of Medicine

Professor of Medicine and Surgery

Chief of Hepatology

Director of Advanced Liver Therapies

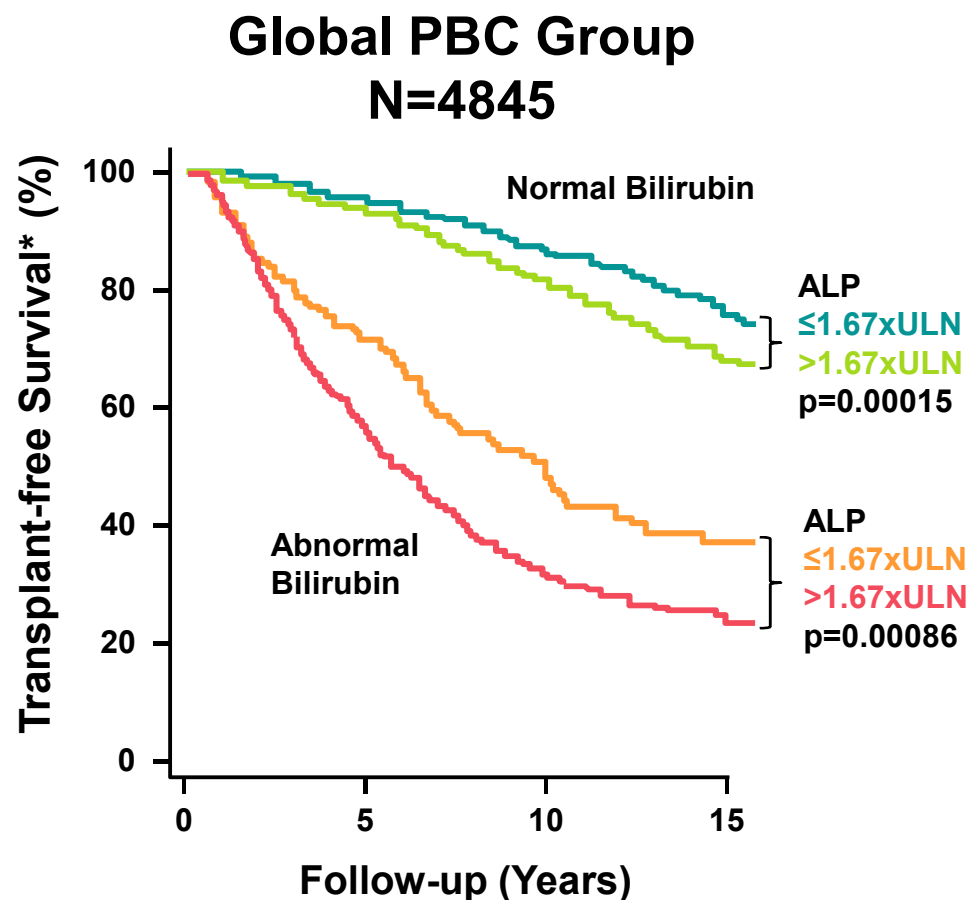
Status Quo of PBC Treatment: 1997-2016



Vision for the Future of PBC Management

- Key attributes of new therapies include
 1. **Targeted for patients with unmet need through appropriate risk stratification**
 2. Proof of benefit in studies of appropriate patient cohorts
 3. Manageable and tolerable side effects

ALP Values Have Predictive Significance in Addition to Bilirubin in Patients with PBC



Double-Blind Phase 3 Inclusion Criteria:

ALP $\geq 1.67 \times \text{ULN}$

or

Bilirubin $> \text{ULN}$ and $< 2 \times \text{ULN}$

Courtesy of Global PBC Study Group and UK-PBC

*Transplant-free survival includes all-cause mortality for Global PBC and liver-related death for UK-PBC.

Vision for the Future of PBC Management

- Key attributes of new therapies include
 1. Targeted for patients with unmet need through appropriate risk stratification
 2. **Proof of benefit in studies of appropriate patient cohorts**
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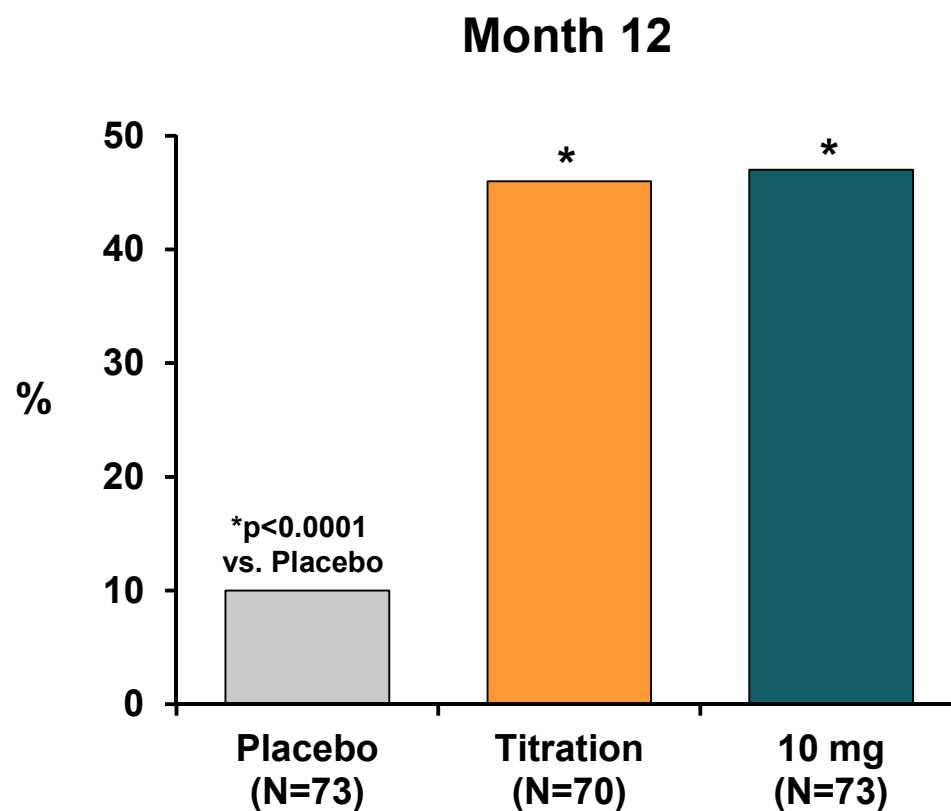
Efficacy of OCA in Phase 3

Primary Composite Endpoint:

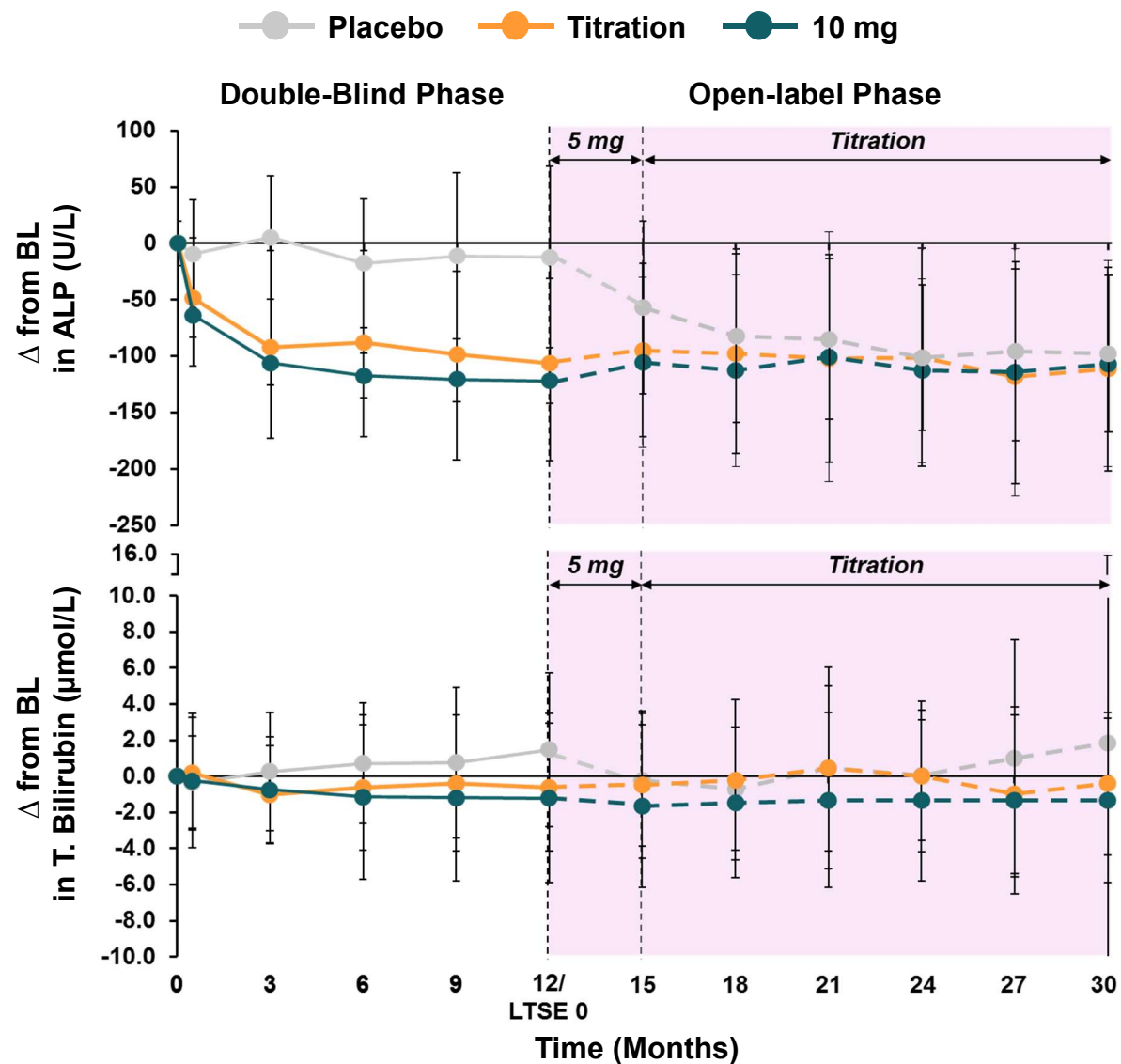
- ALP $<1.67\times$ ULN and
- ALP \downarrow of $\geq 15\%$ and
- Bilirubin \leq ULN

■ Secondary Endpoints

- ALP and Bilirubin
- Markers of hepatobiliary injury: GGT, ALT, AST
- Immune and inflammatory markers



Durability of Response



Vision for the Future of PBC Management

- Key attributes of new therapies include
 1. Targeted for patients with unmet need through appropriate risk stratification
 2. Proof of benefit in studies of appropriate patient cohorts
 3. **Manageable and tolerable side effects**

Pruritus

- Common and distressing symptom
 - Can be managed in most patients
- Pruritus in Double-Blind Phase 3
 - Generally well tolerated with proposed titration regimen
 - VAS comparable among treatment groups after 6 months of therapy and generally mild
 - Substantial group not requiring therapy
 - Discontinuation: 1 patient in titration group
 - Responsive to
 - Interruption/cessation of therapy
 - Alternative day dosing
 - Investigator initiated therapies
 - High voluntary entry into LTSE
- Overall, well tolerated by patients

Changes in Lipids

- PBC associated with hypercholesterolemia
 - Driven by HDL elevation
 - Generally not associated with increased cardiovascular risk
- OCA associated with
 - Reduction in HDL
 - Soon after initiating OCA
 - Maintenance of mean levels within the normal range
 - LDL: transient elevation returning to baseline within 3-6 months

Hepatic Safety Profile

- Overall, clinical hepatic AEs infrequent in treatment and placebo arms
- At the proposed clinical doses (5 mg titrating up to 10 mg once daily) treatment emergent changes in ALT, AST
 - Elevations in OCA treatment arms less frequent than placebo arm
 - Elevations predominantly transient
 - None accompanied by total bilirubin abnormalities

Conclusion – Favorable Benefit-Risk Ratio

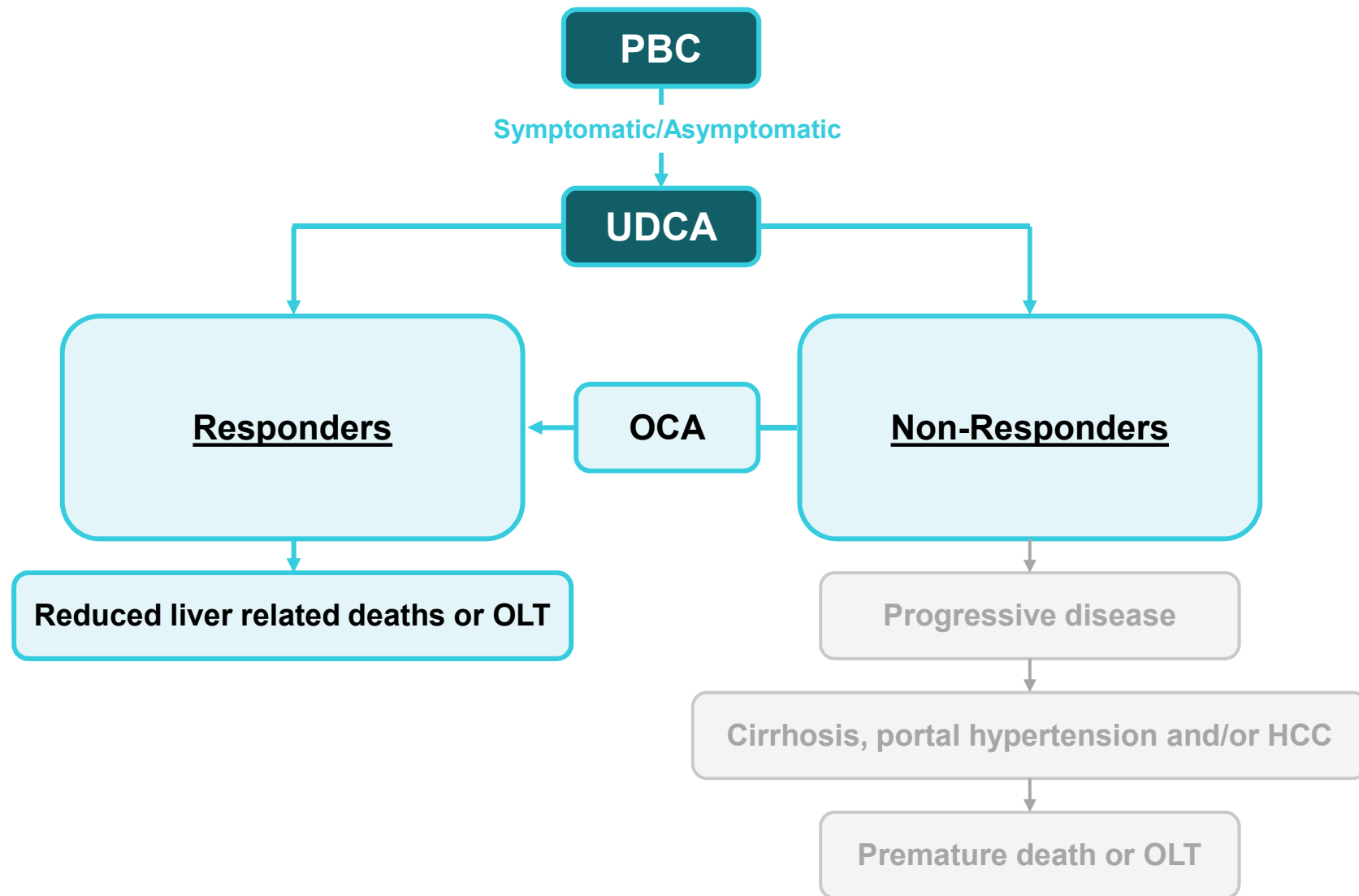
- **Benefits**

- Addresses unmet need in patients non-responsive to or intolerant of UDCA
- Efficacy: OCA met primary and secondary endpoints
- Durability: LTSE confirms durable response

- **Risks**

- Identifiable and manageable
- Adverse events
 - Pruritus
 - Mild HDL reductions and transient LDL increases
 - Infrequent liver related safety observations
- Reversible with discontinuation

PBC Treatment: 2016 Onward



Experts Available for Questions

David Jones, MD FRCP, PhD

Professor of Liver Immunology

University of Newcastle

Institute of Cellular Medicine

Director, UK-PBC Study Group Consortium

John Vierling, MD FACP, FAASLD

Baylor College of Medicine

Professor of Medicine and Surgery,

Chief of Hepatology

Director of Advanced Liver Therapies

Gideon Hirschfield, MA, MB BChir, PhD, FRCP

Senior Lecturer/Honorary Consultant Transplant Hepatologist

Institute of Immunology and Immunotherapy

College of Medicine and Dentistry, University of Birmingham

University Hospitals Birmingham

Kris Kowdley MD FACP, FAASLD

Director, Liver Care Network and Organ Care Research

Swedish Medical Center

Bettina Hansen, PhD, MSc

Senior Biostatistician

Department of Gastroenterology and Hepatology

Erasmus Medical Center

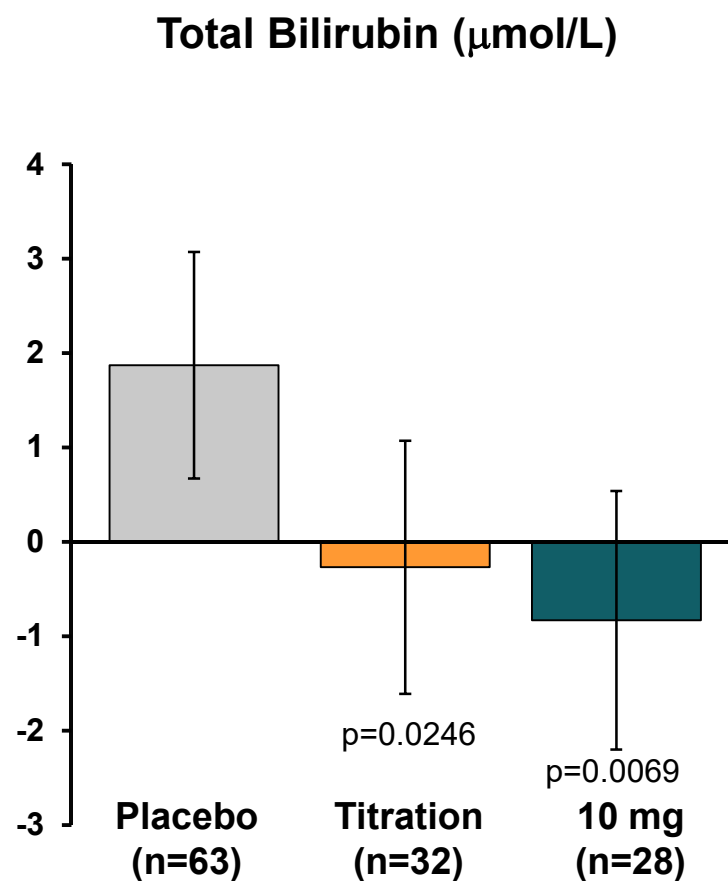
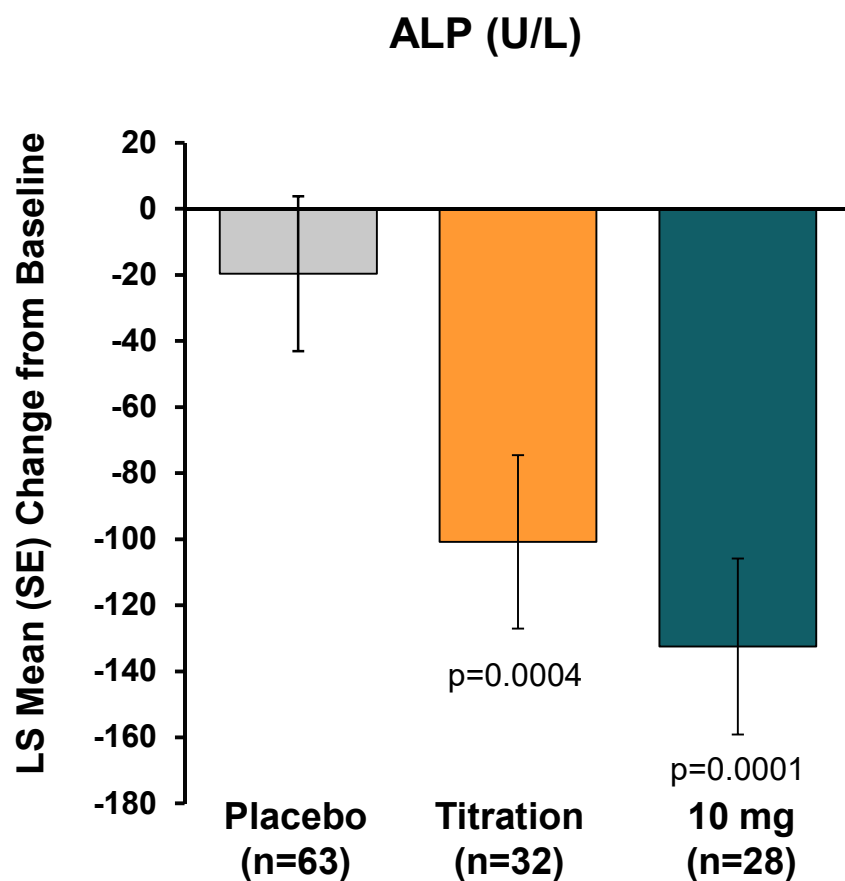
University Medical Center Rotterdam

Backup Slides Shown

Gastrointestinal Drugs
Advisory Committee Meeting

April 7, 2016

Change in ALP and Total Bilirubin: Primary Endpoint Non-Responders Double-Blind Phase 3 – Month 12



P-value for comparing active treatments to placebo is obtained using an ANCOVA model with baseline value as covariate and fixed effects for treatment, double-blind baseline UDCA usage (yes/no) and double-blind baseline total bilirubin ($\leq\text{ULN}/>\text{ULN}$).

Percentage of Subjects Who Met Criteria for Advanced Disease Stage

Double-Blind Phase 3

Criteria For Advanced Disease	Placebo N=73 n (%)	Titration N=70 n (%)	10 mg N=73 n (%)	Total N=216 n (%)
Met criteria for advanced disease	30 (41)	22 (31)	20 (27)	72 (33)
Subjects who met criteria	30	22	20	72
Baseline total bilirubin >ULN	7 (23)	4 (18)	7 (35)	18 (25)
Baseline total ALP >5x ULN	3 (10)	1 (5)	2 (10)	6 (8)
Baseline TE ≥10.7 kPa	17 (57)	13 (59)	10 (50)	40 (56)
Cirrhosis	9 (30)	7 (32)	4 (20)	20 (28)
Medical history of interest ^a	7 (23)	6 (27)	4 (20)	17 (24)

^aIncludes one or more of the following: ascites, hepatic cirrhosis, jaundice, portal hypertension, portal hypertensive gastropathy, and esophageal varices

Optimized Response Criteria Models

UK-PBC Risk Score¹ (2016)

Prognostic index comprising baseline albumin and platelet count, plus bilirubin, ALT or AST, and ALP after 1 year UDCA

GLOBE Score² (2015)

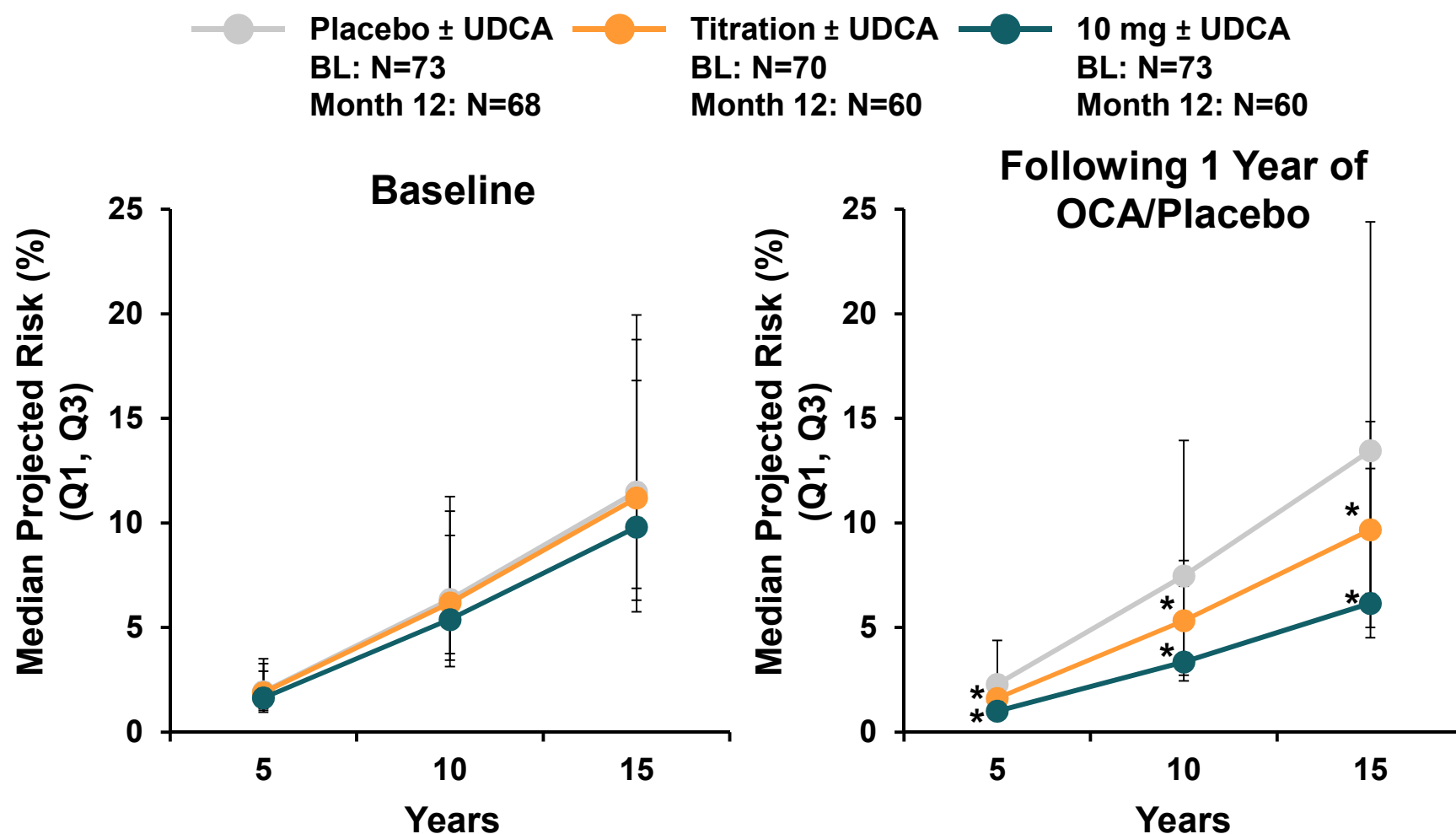
Prognostic index comprising baseline age, and bilirubin, ALP, albumin, and platelet count after 1 year UDCA

¹Carbone M, et al. Hepatology. 2016; 63(3): 697-99.

²Lammers WJ, et al. Gastroenterology. 2015; 149(7):1804-12.

Projected Risk of Liver Transplant or Death Prior to and Following 1 Year of Treatment with OCA or Placebo

UK-PBC

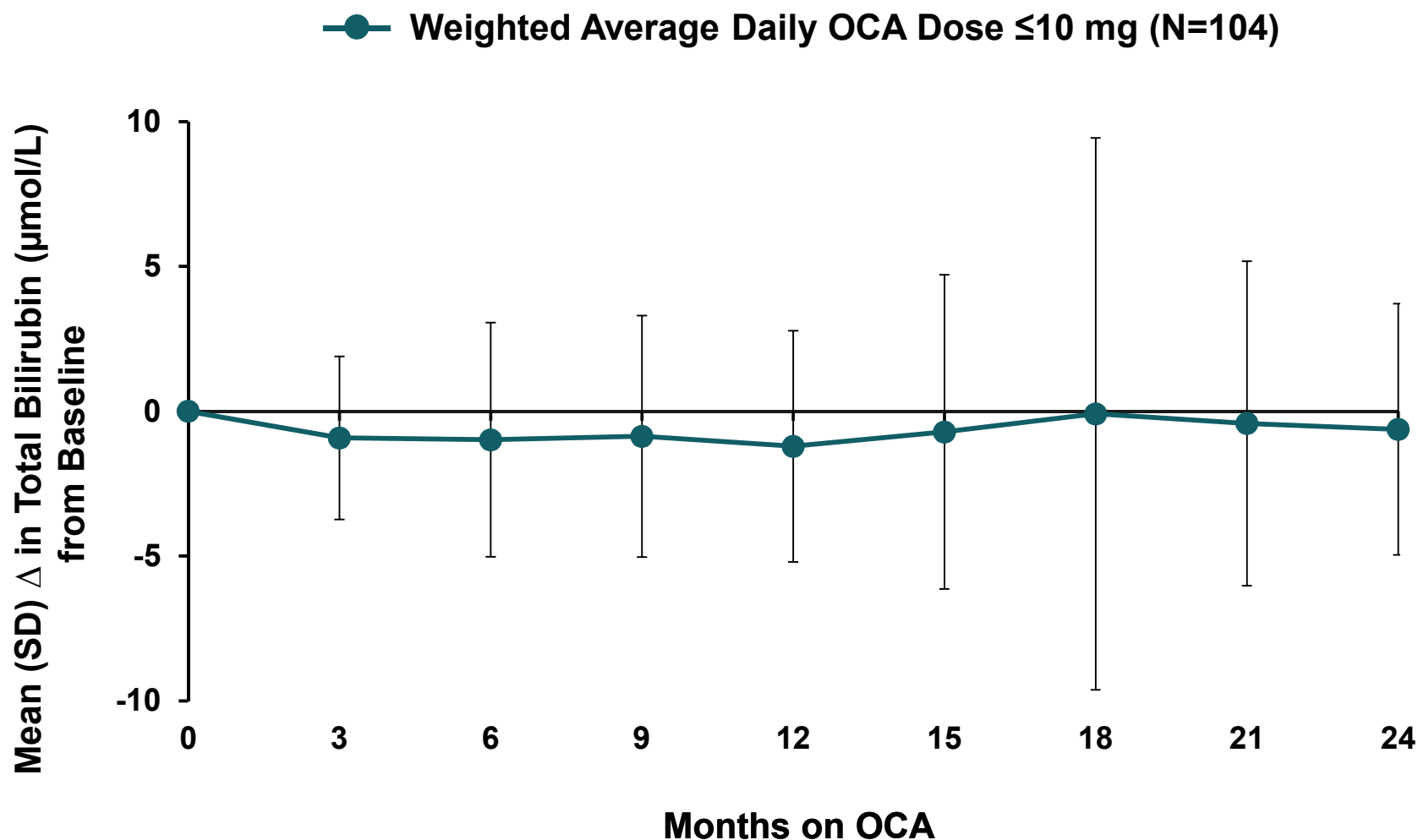


Risk is defined as risk of liver transplant or liver-related death

*p<0.001 vs placebo using rank ANCOVA model with baseline rank as a covariate

Change from Baseline in Total Bilirubin

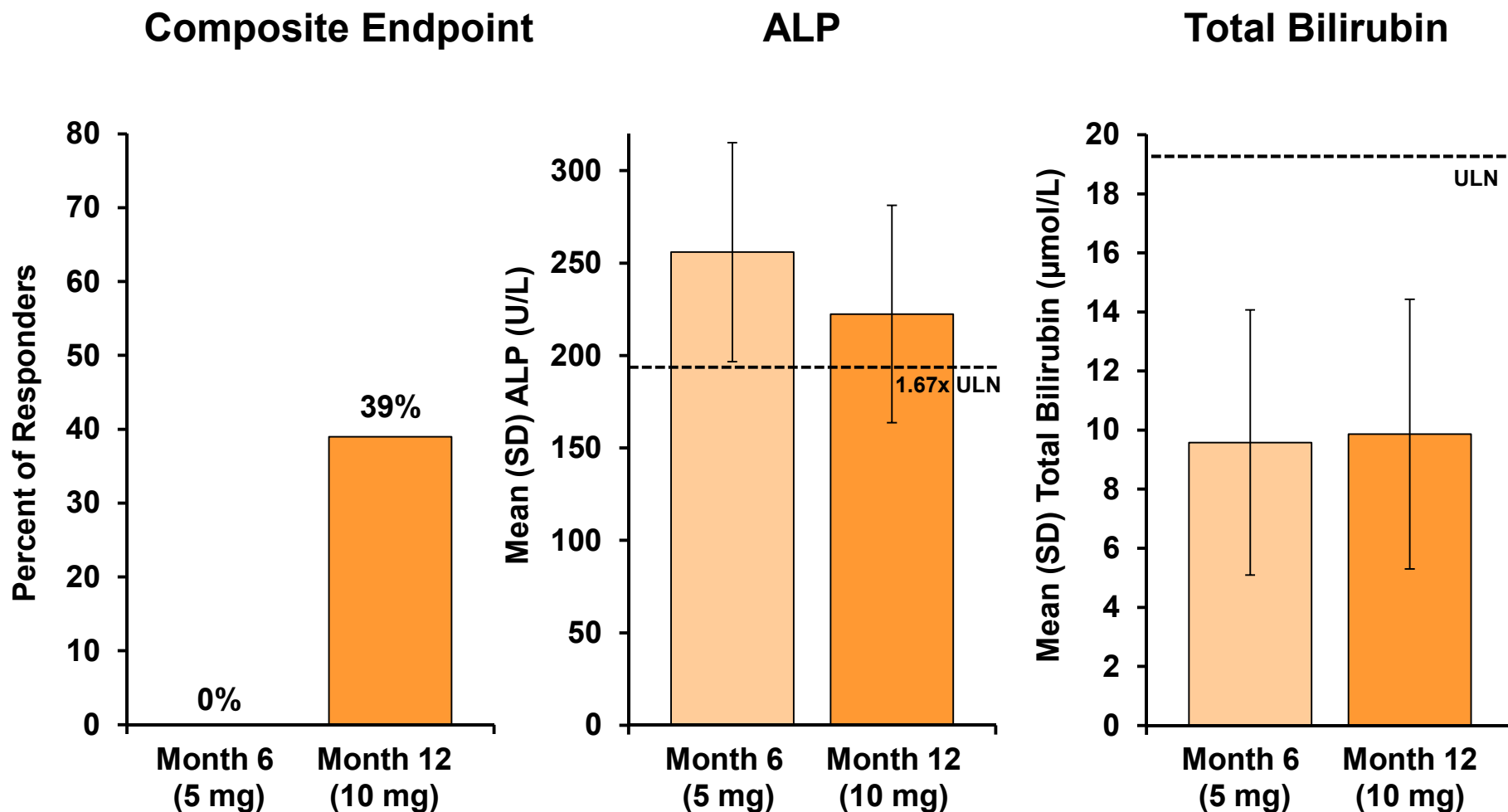
120-Day Safety Update – 2 Year Completer Population



Mean baseline total bilirubin 10.631 $\mu\text{mol/L}$. Data are presented based on OCA baseline.

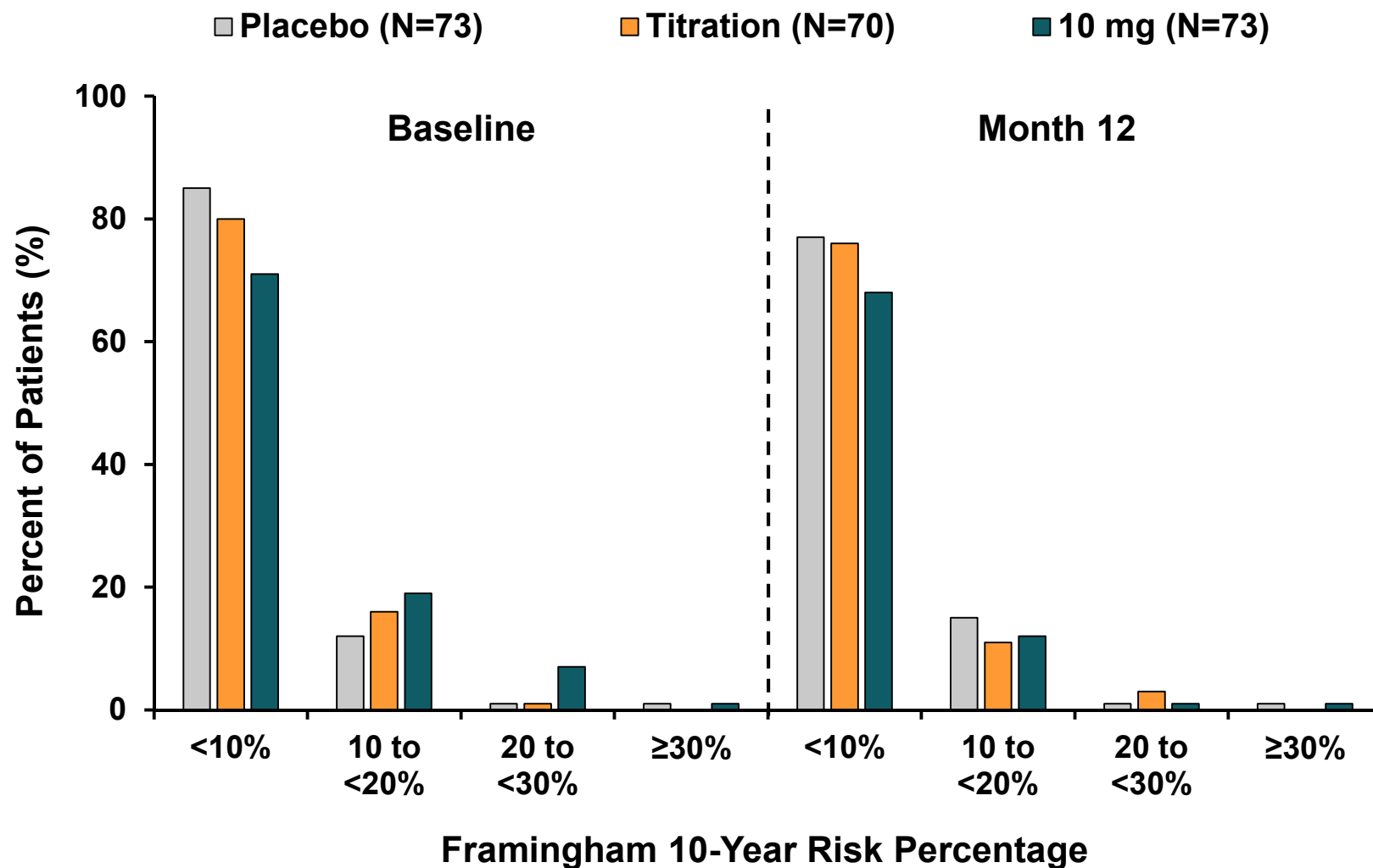
Titration From 5 mg to 10 mg Results in Incremental Benefit

Double-Blind Phase 3 (n=33)

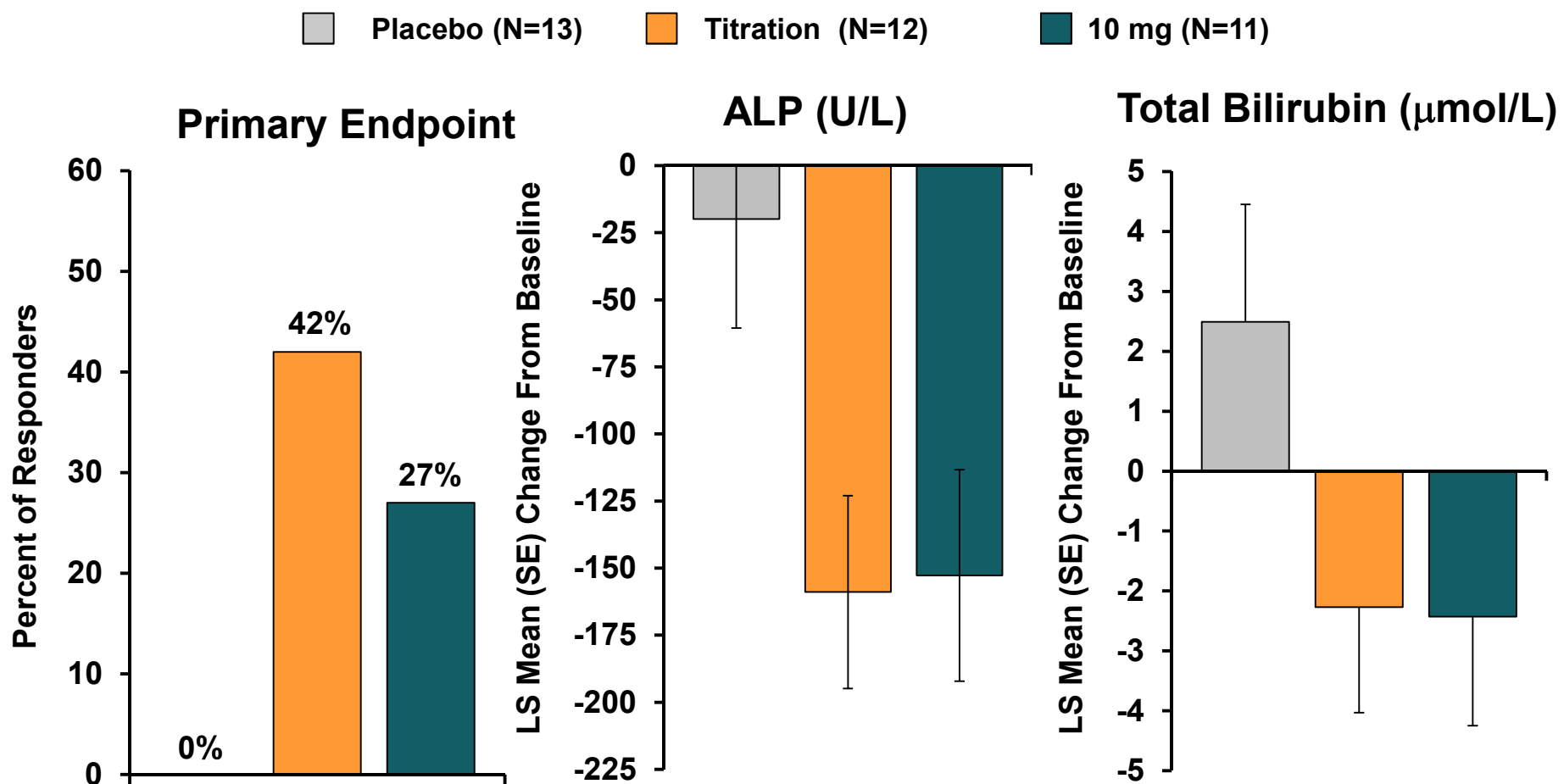


Framingham 10-Year Risk (Assumed Smoker)

Double-Blind Phase 3



Key Efficacy: Rotterdam Pre-Specified Criteria (Moderately Advanced Patients) Double-Blind Phase 3 – Month 12

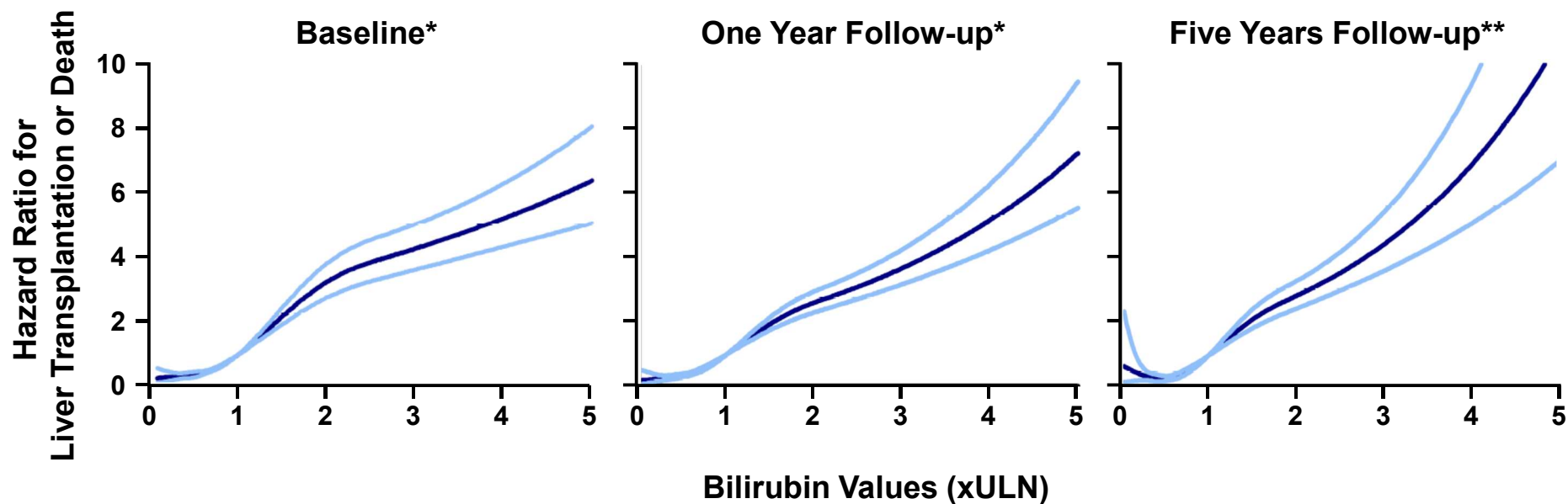


Rotterdam Criteria (moderately advanced): *total bilirubin or albumin is abnormal.*

Hazard Ratios for Liver Transplantation or Death for Bilirubin

Global PBC Study Group

- Log-linear association was observed between bilirubin levels and the risk of liver transplantation and death at baseline and up to 5 years follow-up

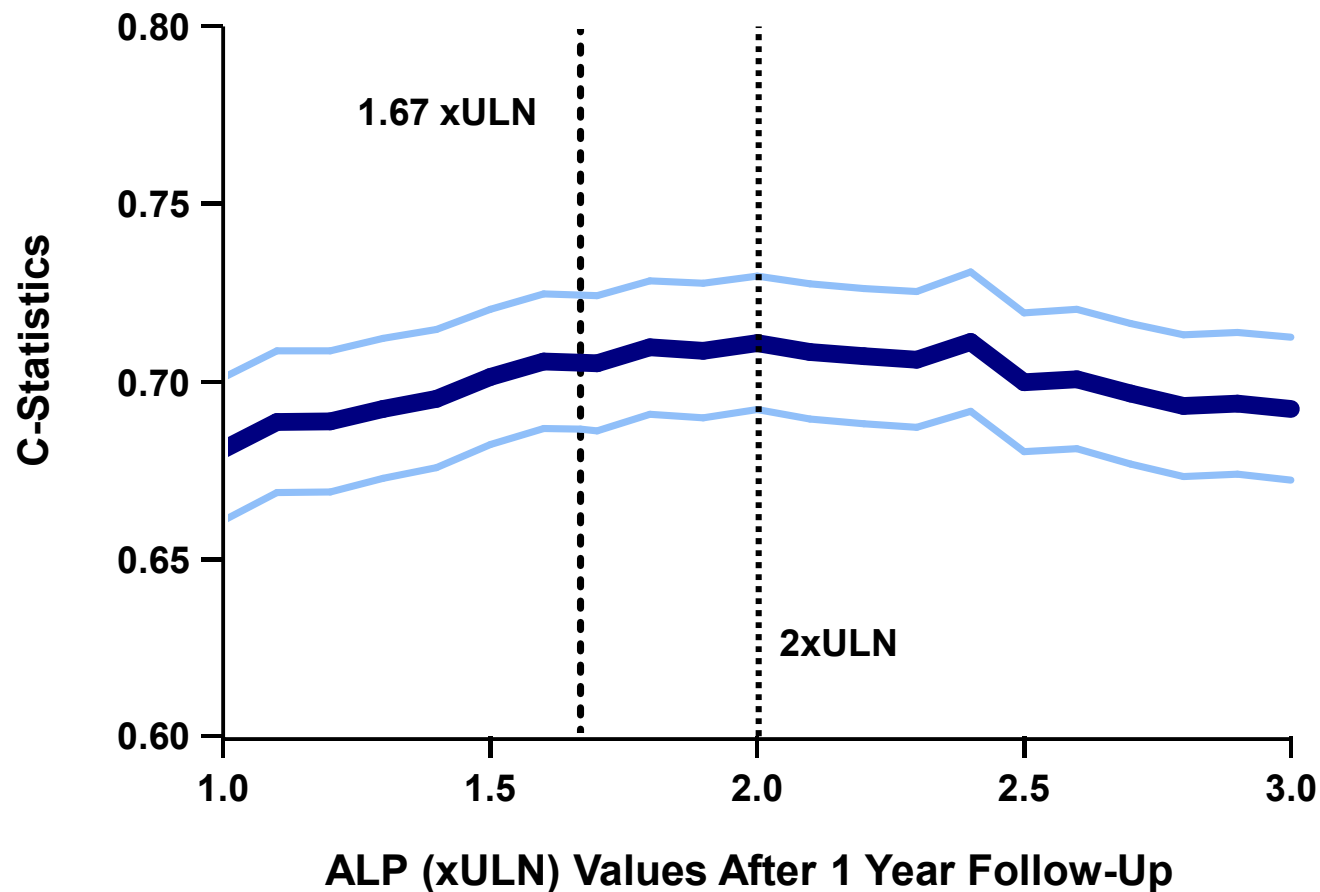


* 3681/4635 patients were included for this analysis

** 2109/3161 patients were included for this analysis

Lammers WJ, et al. Gastroenterology. 2014 Dec;147(6):1338-1349.

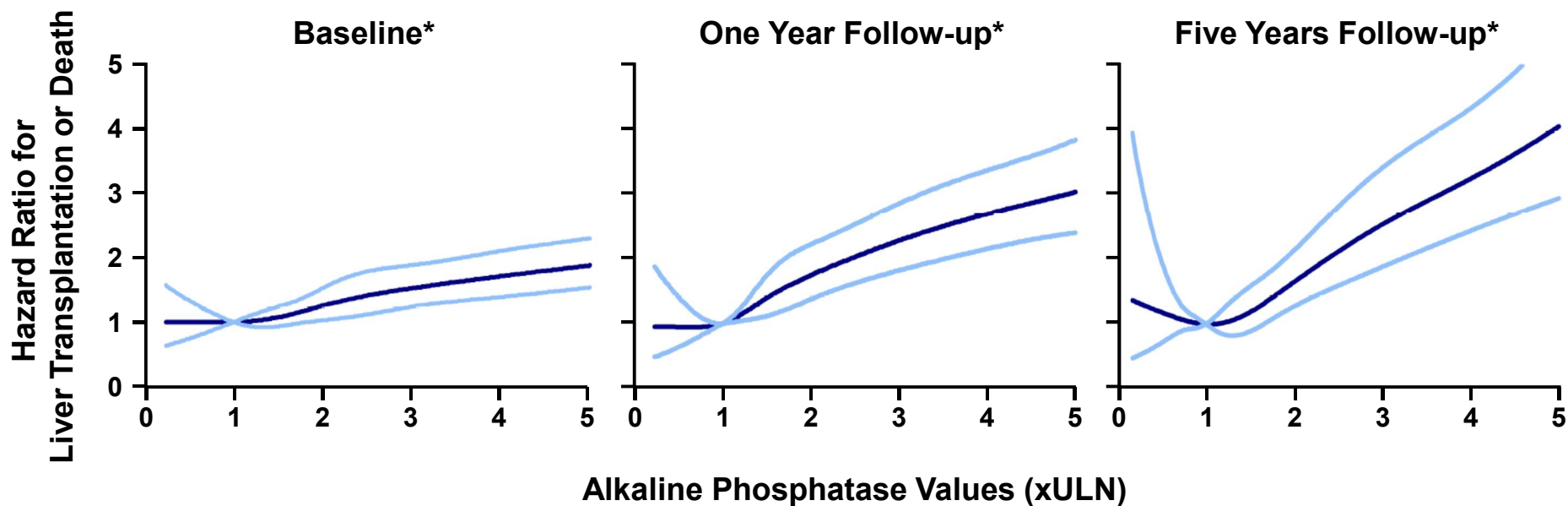
No Clear Optimal Cut-Off Point for ALP



Hazard Ratios for Liver Transplantation or Death for ALP

Global PBC Study Group

- Log-linear association was observed between ALP levels and the risk of liver transplantation and death after 1 year and up to 5 years follow-up**
- Higher ALP levels were associated with reduced transplant-free survival



*3710/4635 patients were included for this analysis

**2203/3161 patients were included for this analysis

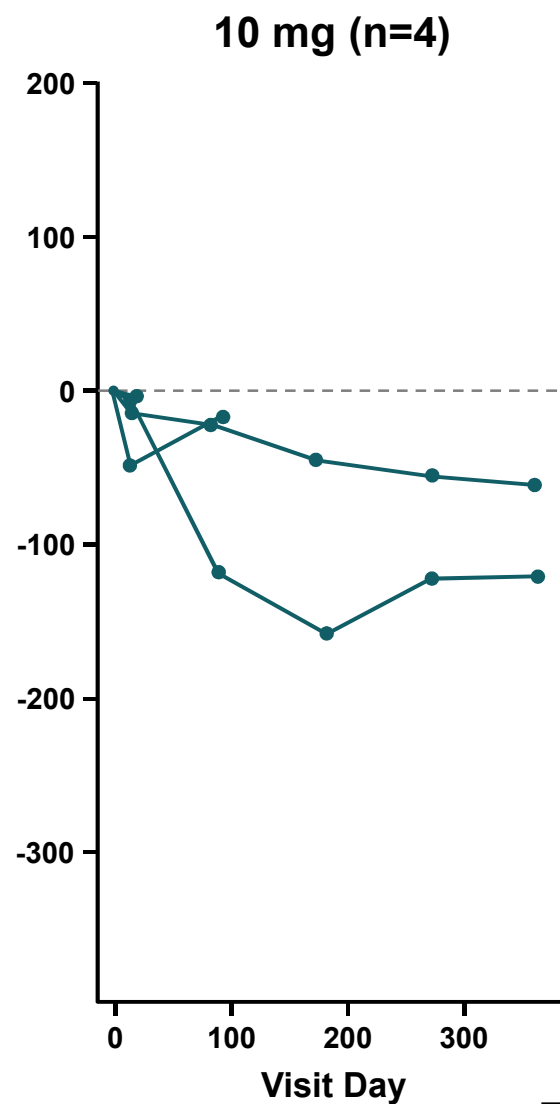
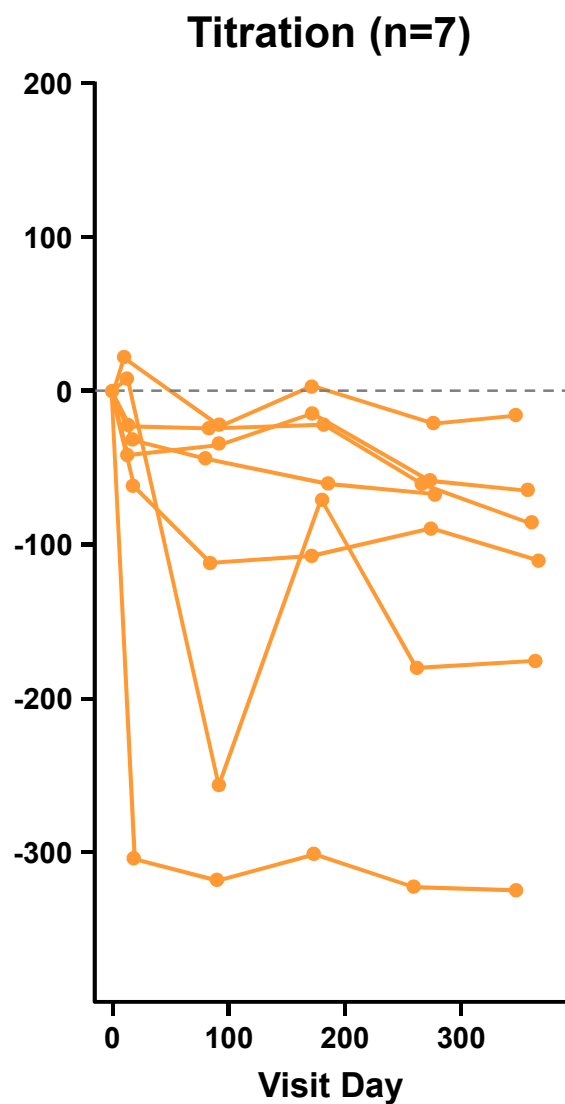
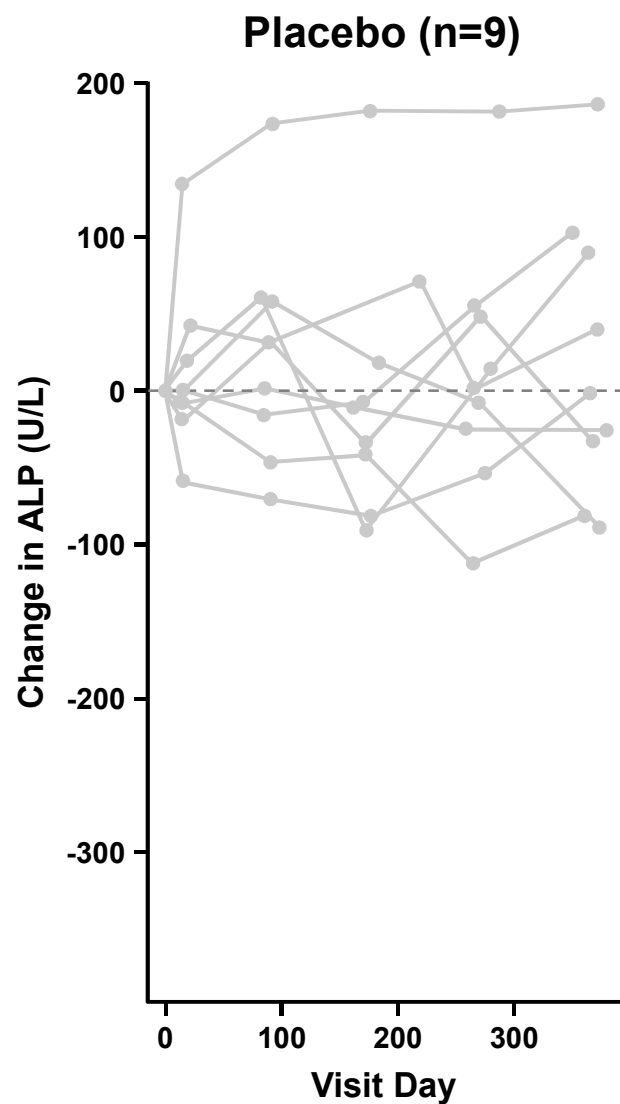
Lammers et al. Gastroenterology. 2014 Dec;147(6):1338-1349.

Summary of SAEs: Patients with Cirrhosis

Double-Blind Phase 3

	Placebo N=9 n (%)	Titration N=7 n (%)	OCA	
			10 mg N=4 n (%)	Total N=11 n (%)
Serious AE	0	2 (29%)	1 (25%)	3 (27%)
Ascites	0	1 (14%)	0	1 (9%)
Erysipelas	0	0	1 (25%)	1 (9%)
Hepatic encephalopathy	0	1 (14%)	0	1 (9%)
Edema	0	1 (14%)	0	1 (9%)
Upper gastrointestinal hemorrhage	0	1 (14%)	0	1 (9%)

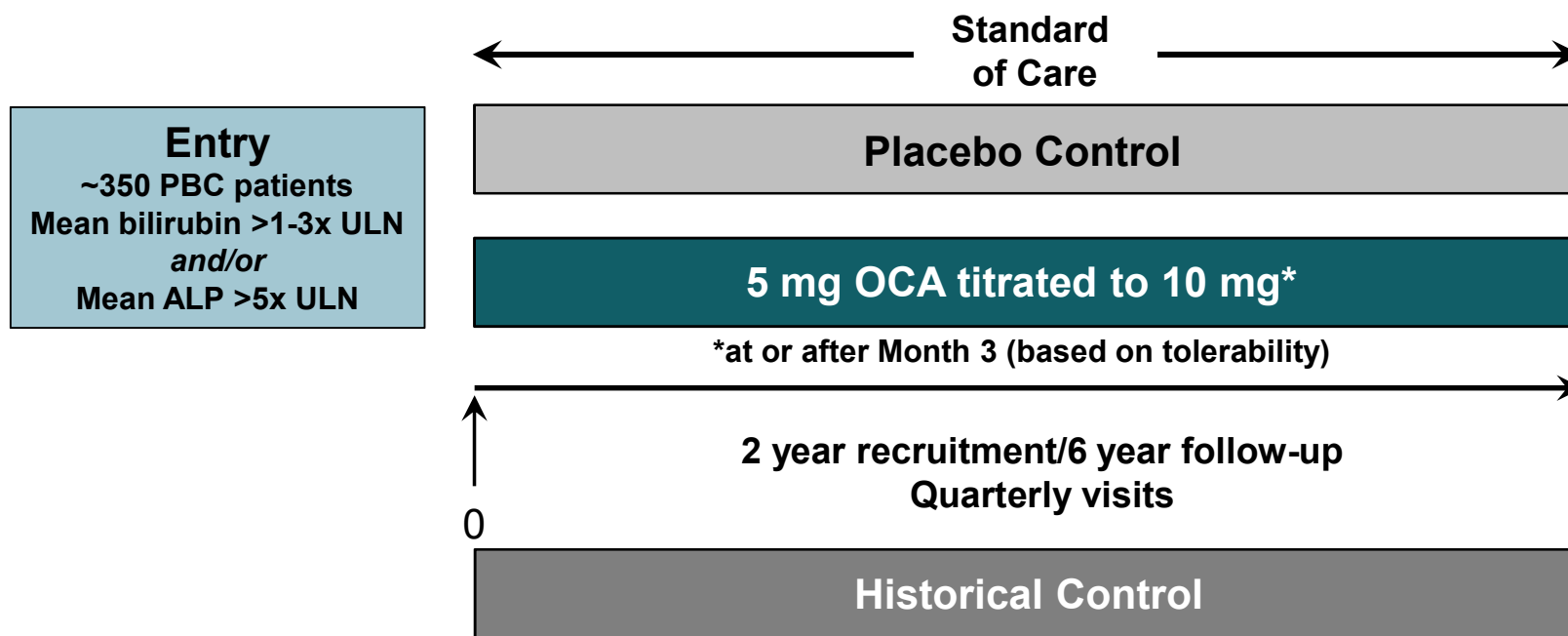
Individual Change in ALP Over Time: Patients with Cirrhosis Double-Blind Phase 3



Study Design

Phase 4 PBC Clinical Outcomes Trial

Study 747-302 protocol was finalized based on feedback from FDA regarding trial design and analysis plan



Primary Composite Endpoint:

Death (all cause), Liver Transplant; or Events related to End-Stage Liver Disease

121 Events (both groups combined)

Provides 80% power to demonstrate statistical significance

Placebo survival estimate of 0.5 at 8 years with assumed hazard ratio of 0.60